THE EFFECT OF LONG TERM TREATMENT WITH DICOUMAROL IN MYOCARDIAL INFARCTION

A CONTROLLED CLINICAL STUDY

BY

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CHAPTER I

Background to this study.

In this study, problems related to long term anticoagulant therapy with dicoumarol in patients after acute myocardial infarction will be discussed.

The isolation (1939) and synthesis (1940) of dicoumarol 3,3′-methylene-bis (4-hydroxycoumarin) by *Karl Paul Link* and his co-workers were soon followed by experiments on the anticoagulant properties of this substance. As early as February 1941, *Bingham, Meyer, and Pohle* published the results of their first experiments on dogs and men, and in June the same year, a similar report appeared by *Butt, Allen, and Bollman.* The prophylactic value in experimental thrombosis was investigated by *Dale and Jacques* (1942), *Richards and Cortell* (1942), *Bollmann and Preston* (1942), *Thill, Stafford, Spooner, and Meyer* (1943), and others. There were soon many reports on the clinical use of dicoumarol as an anticoagulant for prophylaxis and treatment of thromboembolic disease.

Already in 1941, the effect of dicoumarol on a few cases of acute myocardial infarction had been tried. It was not until 4–5 years later that the results of treatment of larger groups of patients were published. *Wright* (1945, 1946), *Nichol and Page* (1946), and *Peters, Geyther, and Brambel* (1946) almost simultaneously published their experiences of treating 76, 44, and 50 cases respectively.

Definite evidence of the effect of treatment was first available from the large, controlled American investigation of 1031 cases, started on the initiative of the American Heart Association in spring 1946 and published by *Wright, Marple, and Beck* (1948, 1954). The results of this well planned and thorough investigation are well known. Briefly, it was shown that anticoagulant therapy with dicoumarol in acute myocardial infarction during the first 4 weeks produces a definite reduction of thromboembolic complications and of mortality. This difference was also verified by autopsy.

These results have been supported by many other publications including *Holten's* (1950, 1951) large combined investigation from hospitals in Denmark and *Tulloch and Gilchrist's* (1950) thorough clinical trial from Edinburgh.

A statistical comparison of the results in 20 controlled investigations, which include a total of about 5,500 cases of acute myocardial infarction, shows that anticoagulant therapy in the acute phase reduces both the incidence of thromboembolic complications and the mortality by about 50 % (see *Wright, Marple, and Beck* 1954, pages 200 and 312).

Short term anticoagulant therapy in acute myocardial infarction has often been criticised and accepted sceptically. The haemorrhagic complications form the main basis for criticism. This is less pertinent now that increased experience of the dosage has reduced the significance of such episodes.

Apart from the question of the danger of haemorrhage, objections have been made to the routine use of dicoumarol in *all* cases of acute myocardial infarction. *Russek et al.* (1951, 1952) and *Russek and Zohman* (1952, 1953, 1954) have, in a series of articles, maintained that anticoagulant therapy is indicated, and is of undoubted value in the more serious infarction cases ("poor risks"). But in the milder cases ("good risks") the thromboembolic complications are so rare, and the prognosis with conservative treatment so good, that the little to be gained by anticoagulant therapy would be more than cancelled by the complications of the treatment. Russek's intermediary point of view has, more recently, been supported by many other authors.

Evans (1954), however, in his attack on the treatment is much more extreme and temperamental. He condemns the large publicity which the treatment has had (see also *Russek and Zohman* 1953), points out on the basis of previous autopsy studies, that coronary thrombosis is only found in 43 % of the cases of acute myocardial infarction, questions the statistical results and concludes: "That anticoagulant treatment in coronary occlusion will go the way of other discarded remedies is certain. Let it go soon. Let it go now, before remorse weighs too heavily on those who may continue for a little time longer to advocate its use."

The indications for anticoagulant therapy in acute myocardial infarction undoubtedly vary from case to case. But, as mentioned by Wright and others, there is, as yet, no certain method of knowing which patients are safe and which liable to thromboembolic complications. The large natural variations in the prognosis of acute myocardial infarction also make it especially difficult to assess the effect of treatment. However, the convincing figures from many well controlled investigations and the effect of treatment theoretically expected cannot be explained away. The authors who doubt or deny the effect of treatment usually base themselves on retrospective investigations, and none of them have given such a good clinical basis as some of the authors who have confirmed the effect.

It is shown in the investigations mentioned that the good results of anticoagulant therapy in acute myocardial infarction depend on the fact that treatment prevents mural endocardial thrombosis, subsequent emboli in the pulmonary and general circulations—and venous thrombosis. One is therefore hardly justified in concluding that this form of treatment also prevents arterial thrombosis, including coronary thrombosis itself, which is in many respects thought to be of a different nature and related to other pathogenetic factors. The evidence for such an effect has previously been very sparse and uncertain, and it is this question that will form the basis of this study.

CHAPTER II

The problem of the investigation. Theoretical and practical considerations for the solution of the problem.

The main question posed in this investigation is the following:

Will continuous anticoagulant therapy after acute myocardial infarction improve the prognosis in a given patient in relation to a similar patient without this form of treatment? In other words: will the long term result of this therapy be a reduction in mortality and in incidence of recurrent infarction and perhaps a decrease in the number of thromboembolic complications?

For those considering starting such an investigation there are many important questions to be answered. The most important of these can be grouped under the following 3 headings:

I. Is there a theoretical basis for expecting such an effect of treatment? We are, in other words, interested in the *pathogenesis of coronary occlusion*, and especially in the aetiological role played by *thrombosis*.

II. Is it possible to solve the problem within a reasonable period of time? In other words: what is the *prognosis* for patients who have survived acute myocardial infarction? Are the number of deaths and recurrent infarctions in the first months and years after a myocardial infarction sufficiently large for it to be possible to show a difference in a reasonably sized controlled clinical trial?

III. Are the necessary conditions present for the investigation to be put into practice?

The two main points here are: (1) Is it possible, in a reasonable time, to collect a sufficiently large number of patients for the material and can it be assumed that these patients will attend the follow-up clinics regularly for observation? (2) Is a dependable and accurate method available for the control of the anticoagulant treatment as a guide for the dosage of dicoumarol?

Each of these questions will now be examined in more detail, and, if possible, answered.

Pathogenesis of coronary occlusion.

Everyone agrees that the primary disease in the majority of cases of myocardial infarction is arteriosclerosis (atherosclerosis, atheroma) of the coronary arteries, which is demonstrated in 90–100 % of the cases. Little is yet known about the aetiology and pathogenesis of arteriosclerosis. All the unsolved problems in this field will not be mentioned here as they have no direct bearing on

the problem of this investigation. It is sufficient to say that there is, as yet, no convincing evidence that anticoagulant therapy prevents or delays the arteriosclerotic process itself. Theoretically, it seems, however, that this might possibly occur, and we shall return to the question later (see p. 20).

Incidence of thrombosis as the cause of coronary occlusion.

Here, the deciding question is: how frequently is thrombosis the immediate cause of coronary occlusion?

On looking for the answer to this question in the literature, the information is very variable. This is certainly primarily because any post mortem investigation into the occurrence of thrombosis in the coronary arteries is very difficult and exacting work. The existing pathological studies have been carried out using different techniques and with varying degrees of thoroughness. However, the incidence of demonstrated coronary thrombosis does not seem to increase with the quality and thoroughness of the investigation, as one might expect.

The most important data from some publications are shown in *Table 1*. These data must form the basis from which to answer our question.

TABLE 1.

Incidence of thrombosis as the cause of coronary occlusion.

Author(s)	No. cases	No. cases with thrombosis	Thrombosis per cent
Wearn (1923)	19	18	95
Nathanson (1925)	113	24	21
Parkinson and Bedford (1928)	40	29	72
Levine and Brown (1929)	46	23	50
Lisa and Ring (1932)	32	13	41
Appelbaum and Nicolson (1935)	150	78	52
Saphir et al. (1935)	34	25	74
Wright-Smith (1936)	495	45	9
Bean (1938)	300	240	80
Horn and Finkelstein (1940)	172	136	79
French and Dock (1944)	80	29	36
Meesen (1944)	590	237	40
Yater et al. (1948)	450	225	50
Papacharalampous and Zollinger (1953)	126	78	62
Wright, Marple, and Beck (1954)	89	64	72
Total	2736	1264	46

These figures show that, in different investigations, the incidence of thrombosis as a cause of coronary occlusion varies from 9 % to 95 %. As mentioned, this probably depends to a large extent on the varying methods and degrees of

thoroughness of the investigations. But this can hardly be the whole explanation. It is probably also partly because of variations in the type of case and in the composition of the different materials.

The incidence of thrombosis seems to be higher in the investigations in which the majority of cases had fully developed myocardial infarction. *Nathanson* (1925) states: "A prolonged attack, consisting of initial shock which the patient survives, is more frequent with a thrombus. Such a picture does occur, however, in coronary sclerosis without thrombosis." The relatively high incidence of thrombosis shown in *Wright, Marple, and Beck's* cases of acute infarction should be remembered here. On the other hand, the incidence of thrombosis shown by *Wright-Smith* was low, although he was especially interested in this problem. His investigation included a very large number of cases of sudden death—244 out of 495 cases—and he himself states that sudden death seldom occurred in the cases with thrombosis. Of the 450 fatal cases in *Yater and co-workers'* investigation, there were 138 cases of sudden death, and a further 130 cases died in the 2 hours after the attack occurred. These authors state: "We find that sudden death without infarction is more common in those with sclerotic occlusion alone, but that death from coronary artery disease is associated with coronary thrombosis in about 50 per cent of the cases."

These data provide the answer to our question, namely that thrombosis does not seem to be the cause of fatal coronary disease in more than about half the cases. There is thus, theoretically, a possibility for a prophylactic effect of continuous anticoagulant therapy, but this effect must be expected to be considerably less than it would have been if thrombosis had been the cause of coronary occlusion in 100 % of the cases.

As mentioned earlier, thrombotic occlusion seems to occur more frequently in cases who have a fully developed myocardial infarct post mortem than in cases who die before there is time for fresh myocardial changes to develop. Therefore, theoretically, one would expect that the difference between treated and untreated cases would be most obvious if we examined the incidence of *recurrent infarction* (fatal or not fatal). The difference in *mortality* between treated and untreated cases would be expected to be less pronounced, as the fatal cases theoretically include a number of cases (sudden death, heart failure, etc.) where the role of thrombosis seems to be less important.

When we assess the prophylactic value of anticoagulant therapy in coronary disease, we must remember other questions, which may be important, in connection with the pathogenesis of coronary occlusion.

Appositional growth of the thrombus.

It is generally assumed that a thrombus is added to and grows in the same direction as the blood stream i. e. venous thrombi grow centrally towards the heart while arterial thrombi grow towards the periphery. The question is, whether

or not arterial thrombi can also grow centrally against the blood stream and thus attack new arterial branches causing an extension of the infarction. It can easily be imagined that a thrombus could form in the stationary column of blood in front of an occluding thrombosis. *Zollinger and Papacharalampous* (1953) have investigated this point in cases of coronary thrombosis. By making serial sections, some longitudinal and some transverse, through thrombosed coronary arteries, they showed that appositional growth in a central direction often occurs with older occluding thrombi. Also on mural non-occluding thrombi they found growth of fresh thrombi, not only peripherally, but also centrally. Similar observations have been made by others studying coronary occlusion and coronary thrombosis in serial sections. The authors point out the considerable theoretical possibilities for anticoagulant therapy in such cases. This conception is also supported by observations published by *Wright, Marple, and Beck* (1954, p. 213). They found clinical signs of extension of the originally infarcted area in 40 of 442 control patients compared with 19 of 589 patients who had anticoagulant therapy.

Recanalisation of thrombus.

There is neither clinical nor experimental evidence to indicate that anticoagulants can cause the thrombus to dissolve or to disappear. On the other hand, there are investigations which indicate that anticoagulant therapy favours the natural tendency to recanalisation of occluding thrombi. In experiments on the ear vein in rabbits, *Wright, Kubik, and Hayden* (1952) showed that, with tromexan, recanalisation occurred after an average of about 3 weeks. In control animals, it was at least 8 weeks, or nearly 3 times as long, before recanalisation could be shown. *Wright and Kubik* (1953) also produced thrombosis in the femoral arteries of rabbits. In the animals who got tromexan, recanalisation occurred after an average of 3½ weeks, and the process started already after 24 hours. The femoral arteries in untreated animals were still occluded after several months.

The role of intimal bleeding in the pathogenesis of coronary occlusion.

The question of the role of intimal bleeding in the pathogenesis of coronary occlusion has had renewed interest in connection with anticoagulant therapy.

Paterson (1936, 1938, 1939) found that vascularisation of the intima of coronary arteries by capillaries direct from the lumen never occurs in normal arteries, but is a usual finding in atherosclerosis. It is especially prominent if occluding thrombosis is present. He found proliferating capillaries in the intima in 15 out of 16 such cases, and it was most pronounced if there was advanced organisation of the occluding thrombus. He often showed bleeding in atheromatous plaques both with and without thrombosis in the lumen of the artery. He relates this bleeding to the capillaries, which are especially disposed to rupture, partly because of the high intra-capillary pressure and the large fluctuations in pressure as a result of the origin of the capillaries direct from the arterial lumen, and partly because of the

poor support the capillaries have in the loose atheromatous tissue surrounding them. The author found intimal bleeding in 32 out of 37 consecutive cases of recent coronary thrombosis, and he maintains that there must be a pathogenetic connection between intimal bleeding and thrombosis.

Paterson's opinion that bleeding in the intima plays a large part in the pathogenesis of coronary occlusion is supported by the observations of many other workers. *Wartmann* (1938) reports 7 cases of fatal coronary occlusion of which 6 were caused directly by extensive sub-endothelial haemorrhage in the intima and haematoma formation with subsequent occlusion. In 1 case the bleeding broke through to the lumen with secondary thrombotic occlusion. He also studied serial sections from 41 occluded coronary arteries, and found that occlusion was caused by an intra-mural haematoma alone in 6 cases, and by a combination of intra-mural haematoma and thrombosis in 14 others.

On the basis of thorough studies of the blood vessel supply to the arterial wall, *Winternitz, Thomas, and LeCompte* (1938) also consider that intimal bleeding is an important factor in the pathogenesis of thrombosis. They maintain, however, like many other authors, that the histological findings are often difficult to interpret: "When a vessel is finally completely filled with granulation tissue, the events leading to the occlusion cannot be reconstructed with any degree of certainty."

Horn and Finkelstein (1940) and *Nelson* (1941) also agree with Paterson and Wartmann that in many cases, intimal bleeding can be the immediate cause of coronary thrombosis.

English and Willius (1943) found bleeding in the intima in 40 % of 135 cases who died of coronary disease. In all the cases where thrombosis was shown in the artery, they also found bleeding in the intima. However, they do not believe that these haemorrhages are the most important factor in the development of thrombosis and coronary occlusion.

Figures from other investigations give intimal bleeding a much less prominent place. *Wright-Smith* (1936) found intimal bleeding as the cause of coronary occlusion in only 1 of his 495 cases, and *French and Dock* (1944) in 5 out of 80 cases (6 %). *Yater et al.* found fresh haemorrhage in 26 (5.8 %) and old haemorrhage in 29 (6.4 %) of 450 consecutive fatal cases of coronary disease. A slightly higher incidence was found by *Papacharalampous and Zollinger* (1953) i. e. 35 (27.8 %) of 126 cases. Of these, however, 21 had simultaneous thrombosis. *Wright, Marple, and Beck* (1954) demonstrated intimal bleeding in only 3 of 89 cases (3.4 %) and in 2 of these thrombosis was the immediate cause of the occlusion. Of 24 cases of recurrent infarction during the observation period, no intimal bleeding was shown either in anticoagulant treated or untreated patients.

It has often been suggested that intimal bleeding in coronary occlusion is a contra-indication to anticoagulant therapy. However, as far as is known, there are no investigations which indicate or prove that this form of treatment provokes an increased number of occlusions of haemorrhagic pathogenesis.

Other pathogenetic factors in coronary occlusion.

The most important pathogenetic factors in coronary occlusion have been mentioned above. But there are other factors that are sometimes of decisive importance.

Müller (1938, 1939) has pointed out that angina pectoris, coronary disease and sudden cardiac death, often in relatively young patients, are common in patients with *xanthomatous deposits*. He stresses that the disease is familial, inherited as a dominant factor, either as clinically demonstrable xanthomatosis or as hypercholesterolaemia. The arteries, and especially the coronary arteries, are the site of predilection for xanthomatous deposits. This familial xanthomatosis—Müller's disease—which seems to be relatively seldom mentioned, is probably a more frequent cause of coronary occlusion and myocardial infarction—especially in the young, than the impression usually given in the literature. Thus, *Waaler* (1956) found such cases in 6–7 % of 275 cases of angina pectoris. How often the xanthomatous plaques themselves in the coronary arteries are the cause of pronounced narrowing, perhaps complete occlusion, and how often there is a secondary thrombosis is, as yet, unknown.

Different types of *arteritis* in the coronary arteries are also of primary significance for occlusion in some cases. The best known example of this is the narrowing of the coronary opening and first 10–12 mm of the coronary arteries, not infrequently seen in syphilitic mesaortitis. Periarteritis nodosa and other types of arteritis can also, rarely, be the cause of coronary occlusion, either alone or as the starting point for thrombotic occlusion. *Papacharalampous and Zollinger* (1953) found arteritic changes in 11 (8.7 %) of their 126 cases, but in 7 of these, thrombosis was a contributory cause of the occlusion.

Rarely, coronary occlusion is caused by an *embolus*, a phenomenon seen especially in bacterial endocarditis.

Finally, it has been maintained that myocardial infarction may occasionally develop without demonstrable narrowing of the coronary arteries. *Gross and Sternberg* (1939) have described 15 cases where they only found moderate atherosclerotic changes in the coronary arteries, but no narrowing or occlusion. A number of factors affecting the myocardial nutrition, including fall in the aortic blood pressure, relative ischaemia due to cardiac hypertrophy, anaemia and reflex vasoconstriction or spasm of the coronary arteries are discussed by these authors. A striking fact, not mentioned by them, is that in 14 of the 15 cases, the myocardial infarcts were not fresh but old and fibrotic. It is therefore possible that there was narrowing or occlusion when the infarction occurred and that the subsequent regressive changes obliterated the most important traces of this.

Is thrombosis a pathogenetic factor in the development of atherosclerosis?

Over a hundred years ago, *Rokitansky* (1852) stated that atheroma was the result of excessive deposition of blood derivatives, especially fibrin, on the inner surface of the arteries. This point of view was strongly questioned by *Virchow*

(1856) who maintained that atheroma was an inflammatory process, and the thickening of the wall was the product of reactive proliferation of the connective tissue cells in the intima.

The more recent general opinion is that atherosclerosis begins as a degenerative change with deposition of fat in the deep layers of the intima, followed by fibrous tissue proliferation.

Duguid (1946) has given new life to Rokitansky's old "thrombosis theory". He has shown that fibrous thickening of the intima with narrowing of the lumen can be the result of a gradual organisation of the occluding thrombi in the coronary arteries. According to Duguid's investigation, such thrombi, by organisation with ingrowth of connective tissue cells and capillaries, shrinking, recanalisation and covering with endothelial cells, can give an anatomical picture indistinguishable from atherosclerosis. A similar organisation also occurs in mural thrombi. The author points out that "white" thrombi, which contain fibrin, are usually completely permeated by connective tissue. On the other hand, "red" thrombi, which contain a large number of tightly packed blood cells besides fibrin, are often only covered on the surface by connective tissue, especially if they are relatively large. Central softening and fatty degeneration occur and result in an anatomical picture confusingly like atheromatous plaques.

More recently, in many new investigations and with new histological material, *Duguid* (1948, 1949, 1952, 1954, and 1955), *Rannie and Duguid* (1954), and *Duguid and Robertson* (1955) have confirmed this opinion.

On the basis of these investigations, Duguid has come to the conclusion that there are two pathogenetically different types of atherosclerosis—cholesterol lesions and thrombogenic lesions. When the lesions are well advanced, it is often difficult to decide which pathogenetic factor was originally responsible. He maintains, however, that the cholesterol lesions, which lead to weakening and gradual softening of the different layers of the arterial wall, usually result in *dilatation* of the lumen. Thrombosis, on the other hand, which occurs on the inner wall of the artery and does not harm the original layers of the wall, leads to *narrowing* of the arterial lumen. Duguid maintains that since it is this narrowing which is dangerous, thrombosis is the pathogenetic factor of most significance in fatal coronary disease.

More recently, many other workers have supported Duguid's opinion. *Harrison* (1948) and *Heard* (1952) produced experimental pulmonary arteriosclerosis in rabbits by injection of finely divided clots into the ear vein. They caused a fibroelastic thickening of the intima indistinguishable from spontaneous arteriosclerosis. *McLetchie* (1952) produced similar intimal changes in the pulmonary arteries by injecting a mixture of Russell viper venom and rabbit brain thromboplastin. *Heard* (1949) has also confirmed Duguid's findings of microscopic fibrin deposits on the intima in the aorta, and has shown the same changes in the first

part of the renal arteries, which are especially liable to atherosclerosis. Similar experiments have also been carried out by *Crawford and Levene* (1952) with the same result.

Geiringer (1951) examined 300 aortas and 100 coronary arteries for vascularisation of the intima. He shows that the normal intima is not vascularised, but nourished from the lumen (see p. 18, Paterson). If the intima increases in thickness beyond a certain limit, the nourishment and oxygen supply will be insufficient. The result is an ingrowth of capillaries into the intima either from the arterial lumen, or through the media from the blood vessel network in the adventitia, or simultaneously in both these ways. Geiringer is in complete agreement with Duguid's thrombosis theory, which, he believes, sheds a new light on these problems. The transmedial vascularisation from the adventitia occurs with the slow gradual growth of the intima beyond the critical thickness. Vascularisation from the lumen, on the other hand, is a sign of a sudden, catastrophic increase in the thickness of the intima due to thrombosis. Demonstration of such vascularisation can therefore, according to Geiringer, be taken as a definite sign of intimal changes of thrombogenic origin. The capillary blood supply to the intima is easily damaged, resulting in infarction, necrosis and scar formation of the intima. Such an area can be the site for secondary thrombotic deposition.

The investigations referred to here suggest that thrombosis is not, as generally thought, only a secondary terminal process in atherosclerosis, but, in many cases, possibly a significant pathogenetic factor for its development. This point of view has not yet been generally accepted. However, it may prove to be a fruitful working hypothesis for further investigations in this important field of medicine. *McLetchie* gives an impression of this in his discussion: "while much remains to be done, a purely thrombogenic basis of atheroma must receive serious consideration." It is certain that, if this is correct, it opens up completely new fields for prophylactic anticoagulant therapy in arterial disease.

Prognosis after survival from acute myocardial infarction.

The second question asked was the following: Is it possible *within a reasonable period* to decide whether or not long term anticoagulant therapy after myocardial infarction has prophylactic value?

There are many publications dealing with the immediate prognosis in acute myocardial infarction, i. e. the prognosis in the first weeks after the infarct. What we are interested in, however, is the outlook for patients who have survived the first month.

More recently, quite a few investigations have been published dealing with the long term prognosis. For an investigation to be able to answer our question, the following conditions must be fulfilled:

(1) All the patients in the investigation must have come under observation *at the latest* 1 month after the attack. Patients who come under observation (e.g. by admission to hospital) at a later stage have already survived for part of the period in which we are interested. If such patients are counted as "observed" from the end of the first month, an error will be introduced as the patients would not have been in the investigation if they had died between the end of the first month and the day of admission. Consequently a too good prognosis will be found. The same is naturally true whether the observation starts from the beginning of the acute attack or 2 or 3 months afterwards.

(2) The diagnosis must have been able to have been made from information available at the end of the first month. If patients were included in whom the diagnosis was made retrospectively, e. g. at post mortem, a bias would arise, in the opposite direction to the possible bias mentioned under point 1. Thus, a too poor prognosis will be the result.

Disregard of these principles is certainly the main reason for the unreasonably large variations found for the "immediate mortality" in the literature. The principles certainly play a lesser part in the assessment of the prognosis, beginning at the end of the first month or later. However, this is difficult to judge as very few workers state the interval between the beginning of the attack and the beginning of the observation period.

In addition to these difficulties often being ignored in the available investigations into the prognosis, the analysis of the data is often incomplete or directly misleading. In many investigations no notice is taken of the fact that the observation period for those who have survived is sometimes very short, so that many patients would probably die before, for example, 3 years had elapsed since the infarct. The influence of age on the prognosis is often not considered. This is often because most investigations are too small to be divided up into homogenous groups without a danger of chance variation influencing the results.

On account of these facts, more detailed mention of the following papers will not be made: *White* (1926), *Parkinson and Bedford* (1928), *Conner and Holt* (1930), *Cooksey* (1935), *Willius* (1936), *Levine and Rosenbaum* (1941), *Rathe* (1942), *Boas* (1951), and *Gertler et al.* (1951).

A brief discussion will now be made of some other publications, which do give some basis for answering our question. Among these, a number of papers published in the course of the present investigation have also been included. The investigations referred to here are, in the author's opinion, sufficient to demonstrate what is known today about the life expectancy in patients who have survived an acute myocardial infarct. The most important data from these investigations are collected in *Table 2*. In a few cases the figures were recalculated by the author so that they could be expressed uniformly for a comparison to be made.

It is clear that the different authors have found considerable differences in the prognosis. The number of survivors after 3 years thus varies from 87 % *(Morris*

TABLE 2.

Prognosis after survival from acute myocardial infarction.

Author (s)	Av. age	No. of cases who survived an acute myocardial infarct and were alive after:			The percentage of these cases alive the following number of years after the acute attack:				
		4 weeks	2 mths.	3 mths.	1	3	4	5	10
Palmer (1937)*	58			212	97	84		74	38
Bland and White (1941)	56	162			81	60		50	31
Katz et al. (1949)	58		353		76	47		22	
Eckerström (1951)	66.7	109			67	41		30	
Sigler (1951)*	55.8	1176						45	11
Waldron and Constable (1951)*	51.6			1551	91			69	55
Morris et al. (1952)*	40-64	119			97	87		82	
Smith (1953)	55.5	85			88	71		64	53
Robb and Marks (1953)* +	51.5			166	93	81	74	70	51
Cole et al. (1954)*	56.7		285					67	44
Westlund and Hougen (1956)	63.1	929			80	60	55		

* The patients included in these investigations had only had one myocardial infarct at the beginning of the period of observation.

\+ In this investigation the length of the survival time was not reckoned from the beginning of the acute attack, but from when the patients were "admitted to disability". (Probably 3 months after the beginning of the attack.)

et al.) to 41 % *(Eckerström)*, and the number of survivors after 5 years varies from 82 % *(Morris et al.)* to 22 % *(Katz et al.)*. The large differences are certainly partly due to the very different age compositions of the different materials. Thus, *Waldron and Constable's* investigation only included patients under 60 years, while the patients were all under 65 in *Morris et al.'s* and *Robb and Mark's* investigations, both of which showed a good prognosis. On the other hand, *Eckerström's* investigation included a large proportion of very old patients. The average age in his investigation was 66.7 years or about 10 years older than most of the other investigations (excluding the 3 with especially young patients mentioned above). Another factor which probably contributed to the large differences in mortality was that some of the investigations (as shown in the table) only included patients with their *first* attack, while others included patients who had had acute myocardial infarction, whether it was the first or a subsequent attack. This last group included *Katz et al.* and *Eckerström's* investi-

gations both of which had a bad prognosis. The variation noted from 4 weeks to 3 months between the start of the attack and the beginning of the observation time naturally also played a considerable part.

Finally, the large differences certainly also depend on the many sources of error and uncertain factors which can influence this type of follow-up investigation, as previously mentioned. Thus, many authors state that their information about many of the patients was incomplete, or that the follow-up was impossible.

A very thorough investigation into the long term prognosis in myocardial infarction has recently been published by *Westlund and Hougen* (1956) based on 1613 patients from 5 medical departments in Oslo. This material has been examined statistically with respect to age and sex. A large number of different subgroups have also been analysed. The authors state: "the mortality ratio (ratio between actual and expected number of deaths) depends to a large extent on age at discharge and number of years after discharge. For instance among males in the entire material the mortality ratio in the first year after discharge varied from 15.5 at ages 40–49 to 4.8 at ages 80–89. Among males 60–69 the mortality ratio varies from 8.1 in the first year after discharge to 2.1 ten years and over". Rough figures making it possible to compare the duration of survival in this investigation as a whole with the other investigations were not given. The figures used in Table 2 were kindly given to the author personally.

In spite of the large variations, the papers referred to give a definite impression that the mortality in the first years in patients who have survived an acute myocardial infarct, is so large that if a form of treatment has any effect, its result should easily be noticeable. On this basis, it should be possible to judge the value of prophylactic anticoagulant therapy within a reasonable period. The large differences in the prognosis from one investigation to the next shows that any attempt to judge the effect of treatment by comparing the prognosis with previous investigations will be of little value.

Cause of death in coronary disease.

A high mortality in itself is not enough on which to base an investigation into the effect of anticoagulant therapy. The question is also, what is the cause of death in these patients? Clinical experience has taught us that in patients who have had a myocardial infarct, the cause of death is usually heart disease. The mode of death can, however, vary—new infarcts, sudden cardiac death or heart failure. These facts should perhaps be illustrated by some figures: Of 45 cases who had survived an acute myocardial infarct by more than 4 weeks, *Hochrein and Schneyer* (1936) found that in 29 % the cause of death was a new infarct, 9 % died suddenly, 9 % had pulmonary embolism, 46 % had heart failure and in only 7 % was the cause not cardiac. *Levine and Rosenbaum* (1941) report on the mode of death in 80 cases who had survived their first acute infarct. Of these, the cause of death in 40 % was a new infarct, 35 % died suddenly, 20 % had heart failure

and in only 5 % was the cause not cardiac. Of 52 cases who died more than 2 months after the acute infarct, *Katz, Mills and Cisneros* (1949) found that in 65 % the cause of death was a new infarct and in 20 %, heart failure. *Sigler* (1951) found, of 393 deaths from coronary disease, that in 68 % the cause of death was coronary occlusion, 16 % died suddenly and 15 % had heart failure. *Cole, Singian, and Katz* (1954) give the cause of death in 171 cases who had survived their first infarct by more than 2 months. Of these, in 55 % it was a new infarct and 17 % had heart failure. Only 10 % of the deaths had no relation to the cardiovascular system.

The largest number of recurrent infarcts after an acute infarct seem to occur in the first years. See e.g. *Conner and Holt* (1930), *Palmer* (1937), and *Cole, Singian, and Katz* (1954).

Practical conditions for the investigation.

Possibilities for collecting material.

The third question asked concerned the practical conditions necessary before the investigation could be started. First of all: would it be possible to collect a sufficiently large number of patients within a reasonable period? Could it be assumed that these patients would attend the follow-up clinics regularly for observation?

In order to answer these important questions a simple numerical assessment must be made of the possibilities available.

The present investigation was planned and carried out while the author was working at Ullevål Hospital, Department VIII. Ullevål Hospital is Oslo City's large municipal hospital and, in 1950, it had 1,920 beds. The hospital has three equally sized medical departments with a total of about 450 beds, i.e. about 40 % of the medical beds available to the 440,000 inhabitants of Oslo.

The patients admitted to these departments nearly all live in Oslo. They can therefore, if desirable or necessary, attend follow-up clinics in the departments and be seen by the specialists working there. Exceptions to this usually only include patients who live out of town or abroad, who are admitted if they need immediate hospital care suddenly while visiting Oslo. Numerically such patients are very few.

This investigation only included patients who had survived their acute infarct by at least 1 month. This point will be returned to later.

The investigation was further limited so that it only included patients who, on admission with their acute infarct, were not yet 76 years old.

In the 3 departments mentioned there were, in 1949, a total of 116 patients (78 men and 38 women) who fulfilled these conditions. Therefore, from these 3 departments one could expect that in about 2 years 200 patients could be collected who would be able to attend regularly at follow-up clinics and perhaps

for treatment. This was considered to be a satisfactory basis for starting the investigation. More details about the collection of the material will be discussed in Chapter IV.

Basis for control of treatment with dicoumarol.

The next consideration to be taken before the investigation could be started was the control of the dicoumarol treatment itself. Unless the control is well planned and dependable and accurate in practice, the basis for assessment of the effect of treatment will be shaky.

The development of anticoagulant therapy in Norway, and especially the extensive use of long term out-patient treatment in this country and in other Scandinavian countries is due, largely, to *P. A. Owren's* fundamental work. Owren's first contributions to this field were based on his basic investigations into the mechanism of coagulation. This is not the place to give a detailed account of these investigations. Some of the main points must, however, be mentioned as they provide the theoretical background necessary to understand the method used in this study to estimate the effect of dicoumarol on the coagulability of the blood. (Owren's PP method.)

Owren's work on the mechanism of coagulation began in April 1943 with the investigation of a 29 year old woman who, since she was 3½ years old, had had a serious haemorrhagic diathesis. She had a considerably prolonged coagulation time and the cause of her bleeding was therefore a serious failure in the mechanism of coagulation. Although the prothrombin time, estimated by Quick's method, was also considerably prolonged, Owren soon noticed that this was not due to lack of prothrombin. However, it took 1½ years of intense and detailed experiments before it was shown that it was due to the lack of a new, previously unknown coagulation factor, and this factor was isolated from the previously known coagulation factors. The new factor was first called the fifth factor *(Owren* 1944, 1947) and later got the name *proaccelerin.*

During these investigations, Owren found that different prothrombin preparations were converted to thrombin at different rates. This difference was not due to proaccelerin, and indicated the existence of another previously unknown conversion factor in the prothrombin preparations used. This factor was temporarily called co-factor V *(Owren* 1947) and is now called *proconvertin (Owren* 1950). It was separated from prothrombin in 1949 *(Owren and Bjerkelund),* but the final proof of its existence came when patients were found who had a haemorrhagic diathesis because this factor was lacking *(Alexander et al.* 1951, *Aas* 1952, *Owren* 1952). Especial interest was focussed on proconvertin in anticoagulant therapy when it was shown that dicoumarol, phenylindanedione and other oral anticoagulants caused a fall in the concentration in the plasma not only of prothrombin, but, to at least as great an extent, of proconvertin *(Owren* 1950).

The discovery of proaccelerin made it clear that Quick's method of prothrom-

bin estimation was not specific, but that the "prothrombin time" estimated in this way was also dependent on the concentration of proaccelerin. *Owren* (1947, pp. 265–271) therefore developed a new "one stage" method of prothrombin estimation. By adding Seits filtered, prothrombin free ox plasma to the coagulation mixture, he made certain of a constant excess of proaccelerin and, at the same time, a constant additional supply of fibrinogen. Prothrombin time estimated with this method is thus independent of the proaccelerin concentration in the plasma under investigation, and the addition of fibrinogen makes it possible to dilute the plasma and still have enough fibrinogen for clot formation. A further modification of the method was described by *Owren* in 1949.

Since, as mentioned above, proconvertin is also necessary for the conversion of prothrombin to thrombin, it became clear that Owren's method was not a specific prothrombin estimation either. It was shown that the Seits filtration of the ox plasma used in Owren's method not only removed prothrombin but proconvertin as well. The method thus estimates the combined activity of prothrombin and proconvertin. It was therefore called the PP method (prothrombin and proconvertin method) *(Owren and Aas* 1951). As dicoumarol (and other anticoagulants) cause a fall in the proconvertin concentration which is at least as great as the fall in prothrombin concentration, it is clear that a method which estimates the combined activity of these two coagulation factors is theoretically very useful as a guide for dose regulation of dicoumarol.

For the details of the method, the reader is referred to the papers mentioned above, but the advantages of the method over the usual "one stage" methods like, for example, Quick's method will be mentioned briefly.

(1) Dilution (1 : 10) of the plasma under investigation increases the sensitivity and accuracy of the method as it allows the most favourable part of the correlation curve to be used, where a difference in percentage concentration gives the greatest possible difference in the coagulation times recorded. This sensitivity applies to all prothrombin concentrations, even those over 100 %. It is therefore possible to follow the initial fall in PP concentration which gives the first impression of the patient's sensitivity. (As is well known, Quick's method is not very sensitive in the range 100–50 % prothrombin.) The dilution also minimises the effect of the different inhibitors and possible variation in the fibrinogen concentration in the plasma under investigation. Errors, which can arise because variations in the haematocrit value of the blood give a difference in the oxalate (or citrate) concentration in the plasma and inadequate recalcification, will also be eliminated by dilution and by the constant, relatively large addition of oxalate (or citrate) in the ox plasma. The presence of small amounts of heparin in the plasma under investigation is also of no significance, and the method can therefore also be used during combined administration of heparin and dicoumarol, often used for the first days after an acute thromboembolic episode.

(2) The method is independent of the concentration of proaccelerin in the sample under investigation, as a high, constant amount of proaccelerin is assured by the addition of the Seits filtered ox plasma reagent. The lability of proaccelerin on standing has therefore no effect in contrast to in Quick's method.

(3) On the other hand, if the estimation is not carried out at once, proconvertin is activated by contact with glass and the PP time is shortened *(Rapaport, Aas, and Owren* 1954). In order to prevent this, Owren now adds a small amount of heparin, 100 γ per ml. in 3.13 % potassium citrate. Mercaptol 1 : 1000 is also added to prevent damage to the sample by bacterial contamination. By using this technique, a correct result can be obtained even if the sample under investigation is 3–4 days old. This can be very important in long term out-patient treatment when patients are not able to attend the clinics personally, and when the samples must therefore be sent by post.

A more detailed account of the reagents used in the PP method and the practical technique will be given later (see pp. 49–52). A more detailed account will also be given of the methods used for administration and supervision of the dicoumarol therapy. The author's personal experience in this field is mentioned in the foreword to this paper.

On this background it was natural to take up the problem of long term prophylactic therapy in myocardial infarction when satisfactory material could be obtained.

Summary and conclusion.

In this chapter the problem of the investigation is presented first. This is followed by an account of the theoretical and practical considerations for the solution of the problem.

On the basis of the literature, the factors in the pathogenesis of coronary occlusion thought to be of greatest interest for the prophylactic value of long term anticoagulant therapy in myocardial infarction have then been discussed. Although not completely exhaustive, the reported data seem to be sufficient to draw the following conclusions:

(1) The pathogenesis of coronary occlusion is closely related to the aetiology and pathogenesis of atherosclerosis, which is, to a large extent, a still unsolved problem.

(2) There are diverging opinions on which process preceeds the morphological changes found in coronary occlusion. In advanced, relatively old changes, most authors agree that no one can be certain of the nature and order of the processes leading to these changes.

(3) Thrombosis (in atherosclerotic coronary arteries) seems, in previously published investigations, to have been the immediate cause of the occlusion in about half the cases. Further, appositional growth of fresh thrombi in a central direction on old occluding thrombi, plays a part in extension of the infarcted area.

(4) Bleeding in the intima can occasionally, in itself, be the direct cause of occlusion. In other cases, such bleeding may be a contributory cause of thrombosis. There is, as yet, no evidence that anticoagulant therapy provokes an increased number of occlusions of haemorrhagic pathogenesis.

(5) There is experimental evidence showing that anticoagulant therapy favours the tendency of the thrombus to recanalisation.

(6) Recent observations suggest that thrombosis may be a significant factor in the pathogenesis of atherosclerosis.

It therefore seems reasonable to believe that long term anticoagulant treatment after myocardial infarction may have prophylactic value: (1) By preventing new cases of coronary occlusion caused by thrombosis. (2) By preventing appositional growth of fresh on old thrombi, and thus hindering the subsequent extension of the infarcted area. (3) By favouring recanalisation of the thrombus and (4) by thus providing better possibilities for the development of collateral vessels.

On the other hand, intimal bleeding represents an uncertain factor in the treatment, about which little is definite at the present.

It seems, however, theoretically possible that treatment can delay or prevent the progression of the atherosclerotic process itself.

The next section deals, on the basis of the literature, with the "late prognosis" after an acute myocardial infarct and the commonest causes of death in these patients. It is pointed out that most recurrent infarcts seem to occur in the first years after the original infarct. It is shown that both the mortality and the incidence of recurrent infarction in the period after an infarct seem to be so high that a controlled clinical trial of reasonable size should be able to demonstrate the effect of long term anticoagulant therapy within a reasonable period.

Taken on the whole, it is theoretically, impossible to make any calculation or definite statement at all on the prophylactic value of long term treatment after myocardial infarction or in coronary disease in general. The only way to evaluate the treatment is to start a controlled clinical trial, the results of which can be assessed statistically. There is thus good reason to suppose that the investigation planned will serve a useful purpose and be of value for the solution of our problem. The answers to the many questions on the mechanism of coronary occlusion may then come in second place.

In the last section of this chapter, it is shown that there were good opportunities for collecting a sufficiently large number of patients who would be able to be under continued supervision. Further, an account is given of the theoretical background for Owren's PP method for estimation of prothrombin and proconvertin, which, in this study, is the basis for control of the antithrombotic effect during treatment. Thus, the practical conditions were present for starting the investigation.

CHAPTER IV

Planning the investigation.

As mentioned in Chapter II, the object of this investigation is to assess the prophylactic value of continuous treatment with dicoumarol of patients after acute myocardial infarction. It must be stressed that the effect of anticoagulants in the acute phase of the disease has no bearing on this problem. In 1950, when this investigation was planned, this question had already been the basis of thorough investigations which seemed to establish the value of such treatment (see pp. 13–14).

This investigation was therefore planned as an observation of patients who had survived their acute infarct by at least 1 month. It was further agreed that all the patients should have anticoagulants during the first month after admission. Thus, none of the patients were deprived of a form of treatment the effect of which seemed to be established already. It was also obvious that all the patients should have as uniform treatment as possible in the interval between the acute attack and the beginning of the observation period. If no anticoagulants had been given, for instance to all the patients in the control group, a bias might have developed, probably in favour of the control group, as the treated group would thus include a larger number of serious cases who had survived their acute infarct thanks to anticoagulants.

Allotting patients to the treated and control groups.

Choice of statistical method of selection.

The first requirement when the effect of a form of treatment in a controlled clinical trial is to be assessed, is that the groups to be compared are uniform before treatment (observation) begins.

A large number of variables can influence the late prognosis after acute myocardial infarction. These include age, sex, past history especially as regards previous infarction, heart failure, hypertension, enlarged heart—and, finally, the severity of the infarct recorded with its effect on the function of the heart, to mention some of the most important. It is therefore essential that these factors affecting the prognosis should be as evenly distributed as possible between the two groups to be compared, so that the groups are comparable from a prognostic point of view at the beginning of the investigation.

Different methods of allotting patients to treated and control groups come to mind when one is planning a therapeutic trial, and a few of them will now be discussed.

It might be thought advantageous to grade (stratify) the patients into prognostic groups (strata) before allotting them to treated and control groups. In other words, on the basis of a great many variables, some of which are mentioned above, an assessment and grading of the prognosis according to fixed criteria would have to be made in each individual case. All the patients in the same prognostic stratum would then, for example by drawing lots, be distributed between the treated and control groups.

Such a method of approach would entail a great deal of extra work, and considerably complicate the subsequent statistical analysis. In addition, the prognosis after myocardial infarction is very difficult to predict. Assessment is moreover, complicated by errors of a subjective, psychological nature. A very important practical difficulty is also that the patients to be stratified according to prognosis are not all present at the beginning of the investigation, but they come up one by one in the course of several years. Finally, the method cannot be used without another important difficulty cropping up that will be mentioned below. On the whole, this method of approach seems ill suited to this investigation and offers no advantages.

A chance distribution of the patients to the treated and control groups without previous stratification can be carried out in different ways: for example, the patients can be allotted to the two groups alternately in the order they are admitted to hospital. Or, they could be allotted according to whether they were admitted on even or odd dates, or on the basis of the date of birth being even or odd. The latter method would probably be the safest (see, for example the skew distribution in *Wright, Marple, and Beck's* large investigation in which the method of even and odd dates of admission was used).

The use of one of the methods mentioned here also entails certain practical difficulties. The main reason for rejecting such a method of approach in this investigation was, however, different. Right from the beginning it was obvious that one of the greatest difficulties in the investigation, which would last for several years, would be to keep the control group intact. In other words to keep the patients in this group free from long term anticoagulant therapy.

Any new treatment is, in the eyes of the public, always the best, and there was reason to fear that, as the patients in the control group gradually got to know that some patients were treated in this way, they would want the same themselves. The significance of this in relation to allotting the patients will be mentioned: In the medical departments in this hospital the patients are not in single but in larger rooms with 2 to 7 beds, and, in each department there is a large ward for 22 patients. It is therefore inavoidable that two patients admitted for acute myocardial infarction are often in the same room. During a month's

stay in hospital there would be ample opportunity for discussing and getting to know about their disease. It would then be very difficult to explain to two such patients that although they had the same treatment in hospital, their treatments would differ after discharge. For this reason, which in the author's opinion is very real and important, allotting the patients by even and odd dates of birth was rejected. As indicated before, the same difficulty arises in connection with prognostic stratification of the patients which was also rejected for other reasons.

The method of allotting patients found, on careful consideration, to be the best was to let the question of which group a patient was included in depend on to which department he was admitted. This method could be used as nearly all the patients with acute myocardial infarction were admitted to hospital as emergencies. Such admissions occur in the same way in all the municipal hospitals in Oslo. The doctor wanting the admission contacts a *hospital bed service outside the hospital.* This agency is given the number of empty beds in each of the three medical departments every day. Between 8 am and 7 pm they decide to which department an emergency shall be admitted. From 7 pm until 8 am the next morning the patients are admitted alternately to the three departments so that the night work is shared between their staff.*

Question of the use of placebos.

In many of the recent controlled clinical therapeutic trials, the well known placebo technique, sometimes in the form of a "double blind test" has been used.

The question of a placebo treated control group was also considered in this investigation, but was rejected for the following reasons: the use of placebos would mean that all the patients in the control group would have to attend clinics regularly every 1–3 weeks, have a venepuncture, and, on a fictitious basis, get a given dose of the placebo. This would have to go on for several years. How far a doctor, even with an ideal motive, is justified in interfering in the life of a patient and fellow being is a very difficult question both from the ethical and legal points of view. This investigation was carried out by one individual and a "double blind test" with the possible additional certainty of placebo treatment was therefore impracticable. The ethical side of the question also thus comes into sharper relief as the responsibility for the additional load on the patients would rest on the author personally. One cannot help thinking of the demoralising effect if, for years, a doctor has to act to his patients and knowingly deceive them.

* (The only exception to this are a few patients referred directly by the physicians in the departments. Numerically such patients were very few. There is also no reason to suppose that patients with acute myocardial infarction in this category would vary from department to department.)

On the other hand, it is doubtful whether use of placebos would give very much safer results in an investigation like the present one. The first things to be compared in this investigation are objective phenomena such as the occurrence of recurrent infarcts and the number of deaths in the two groups. Such phenomena hardly depend on suggestion or on the subjective feelings of the patient.

The precautions taken so that the patients in the treated and control groups would have as similar cardiological treatment and supervision as possible, apart from the use of anticoagulants, will be discussed in more detail later.

Age limit.

Very old patients are usually frail and find it difficult to get about, so it is often impossible for them to attend the out-patient clinics. It was therefore decided to limit this investigation so that it only included patients who were not yet 76 years old when admitted for their acute infarct.

Size of treated and control groups.

In a controlled clinical trial it is usually best if the groups to be compared are of approximately the same size. The method of allotting patients used in this investigation made it necessary for this question to be considered. As mentioned, the patients were from three equally large medical departments, each with about 150 beds. The number of patients treated every year for acute myocardial infarction varied slightly in the different departments for the following reasons: Dept. IX is the only one which treats patients with pulmonary tuberculosis and such patients occupy about 40 of their beds. Depts. VII and VIII are more similar as both are general medical wards. During this study, however, metabolic and digestive system diseases tended to be the main interest in Dept. VII, while cardiovascular diseases were the main interest in Dept. VIII. This lead to a certain moderate bias in the type of cases admitted. This fact will be illustrated by the following figures for the number of patients under 76 years old with acute myocardial infarction in each department, who, in 1949 (the year before the investigation was planned) survived their acute attack by more than one month: Dept. VII: 41 patients, Dept. VIII: 47 patients, and Dept. IX: 28 patients. Total 116 patients. It was therefore decided to allot the patients to the treated and control groups in the following way: for all the patients admitted to Dept. VII, anticoagulant therapy would be stopped after one month and the patients assigned to the control group. All the patients in Dept. VIII would get long term anticoagulant therapy. The patients admitted to Dept. IX would, for alternating periods of about half a year, be treated either as patients in Dept. VII and assigned to the control group, or as patients in Dept. VIII and assigned to the treated group. Dept. IX would be told when to change treatment by the investigator who tried to make the groups as equally sized as possible.

Patients who had to be withdrawn from the final investigation.

When the investigation was planned, it was clear that some of the patients who satisfied the requirements mentioned, would not be able to go through with the regular out-patient control. It was reckoned that patients would have to be withdrawn for the following main reasons: (1) Severe clinical heart failure. (2) Severe complicating disease with a bad prognosis or very reduced mobility. (3) Mental disease or severe psychic debility. (4) Contraindication to use of anticoagulants. (5) Geographical conditions. (6) A combination of these factors, or others giving rise to reduced mobility or complete invalidism.

The patients in the control group who, for the same reasons would not have been able to have had out-patient treatment with dicoumarol, also had to be rejected. The question of exclusion from the investigation was usually taken up with the doctors in the appropriate department, who knew most about the patient. The final decision was, however, made by the investigator with the above factors in mind. The number of such cases and the reason for their exclusion will be mentioned later.

Clinical investigation of the patients while in hospital.

For any clinical study which is planned to start by collecting patients who will be subsequently under observation for some time, it should be possible for the investigation of each individual case to be the same. All those who have attempted clinical follow-up studies on the basis of old case histories know how disheartening it is to hunt in vain for important information. In the present study an effort was therefore made so that all the patients should have the same clinical investigations as far as possible, right from the time of admission. It was borne in mind that the patients would be from 3 different medical departments, and that many different doctors would take part in the examination of the patients and the taking of case histories. The author considered that the clinical investigations required should not be so numerous and time consuming that it might be difficult to carry them out. They should therefore not be too different from those normally carried out in the 3 departments on a patient with acute myocardial infarction.

At the start of the investigation, the following schedule was worked out for the medical investigation of the patients and issued to the relevant doctors:

Case history.

The case history must, as far as possible, contain information about previous: (1) hypertension, (2) angina pectoris, (3) infarction, (4) prodromal symptoms of infarction, (5) heart failure, and (6) whether the present infarct occurred when the patient was resting or exerting himself.

Clinical examination.

The clinical examination must include looking for: (1) pericardial friction, (2) gallop rhythm, (3) signs of shock, (4) signs of heart failure (dyspnoea, cyanosis, congestion of the liver, peripheral oedema), and (5) signs of xanthomatosis (xanthomatous nodules and xanthelasma).

Investigations.

The following *investigations* must be carried out on all patients: (1) pulse counted every morning and evening, (2) temperature taken every morning and evening, (3) blood pressure taken daily the first 3 days, thereafter once a week, (4) electrocardiogram to be taken in the first days as often as necessary for diagnosis and treatment, and again just before discharge, (5) height, (6) body weight, and (7) X-rays of the heart to determine cardiac volume before discharge.

Laboratory investigations: (1) white blood cell count on the first 3 days (after admission or after the attack), (2) BSR on the 1st, 3rd, and 5th days and later once a week, (3) fasting blood sugar the day after admission (infarct), (4) serum cholesterol, and (5) PP value of blood before anticoagulant therapy started.

This schedule was considered to contain the minimum requirements and was naturally supplemented if the diagnosis or, more especially, the treatment made it necessary.

A similar but rather more simple schedule was duplicated and issued to the nurses in the 3 departments, and kept handy in each ward. The senior nurses also attended a meeting where the most important features of the investigation were gone through in more detail, and the significance of a complete investigation was emphasised.

In order to make it even more simple, forms were made to hang on the back of the temperature charts of all patients with certain or probable acute myocardial infarction, showing the tests to be carried out, so that they could be crossed out as they were done. Finally, a schedule was sent to the laboratory staff which informed them when an infarction patient was admitted and reminded them which laboratory investigations should be carried out while the patient was in the ward.

This regime worked very well and made certain that the patients had a fairly uniform investigation, as will appear later.

Diagnosis of the acute infarct—diagnostic criteria.

The primary requirement before the patients could be included in this investigation was that, while in hospital, they should have definite signs of *a recent acute myocardial infarct.* All cases in which the diagnosis was in doubt were excluded, an no case was included unless the doctor in charge of the daily treatment and the investigator agreed on the diagnosis. The diagnostic criteria used to make the diagnosis were the usual ones:

(1) Attack of pain of typical character and localisation.
(2) Typical electrocardiographic changes which gradually alter during the course of the disease.
(3) Pericardial friction rub.
(4) Raised temperature.
(5) Leucocytosis the first days after the attack.
(6) Increasingly raised BSR the first days after the attack.
(7) Considerable fall in blood pressure the first days after the attack.
(8) Signs of shock: paleness, sweating, feeble rapid pulse and severe fall in blood pressure.
(9) Tachycardia with a pulse rate of 90 or more the first days after the attack.
(10) Signs of left heart failure with dyspnoea, clinical (and/or radiological) signs of pulmonary congestion and possible pulmonary oedema.
(11) Raised fasting blood sugar during the first 24 hours after the acute attack.

There was no doubt about the diagnosis from the clinical investigations in any of the cases included in the clinical trial. That the diagnostic criteria were strict enough is demonstrated by the fact that signs of previous infarction were present in all the 43 patients who later came to post mortem.

Investigation technique.

The laboratory investigations carried out while the patients were in hospital, were done in the clinical laboratories attached to each of the 3 departments. During the follow-up of the patients, these investigations were all done in Dept. VIII. Some of the techniques used are described below.

Quantitative estimation of prothrombin-proconvertin. Owren's PP method.

The quantitative estimation of "prothrombin" was carried out using Owren's PP method which really estimates *the combined effect of prothrombin and proconvertin.* The method was originally described by *Owren* in 1947 (pp. 265–271). It was later slightly modified, see *Owren* (1949) and *Owren and Aas* (1951). The theoretical basis for the method and its theoretical and practical advantages have previously been discussed in more detail in this paper (see pp. 27–29).

The method was introduced by the author into the 3 medical departments in Ullevål Hospital in the spring and early summer of 1950. All the details of the method were supervised and the laboratory nurses in the 3 departments were trained in the technical details by the author personally. The thromboplastin extract and the prothrombin and proconvertin free ox plasma reagents on which the method is based, were produced by the author in the clinical laboratory of

Dept. VIII, and the chemical reagents by the central laboratory for medical physiological chemistry in Ullevål Hospital. The method used for extraction of the reagents was as follows:

Thromboplastin.

Thromboplastin was extracted from human brain in the following way: the brain was freed from pia and blood vessels and the blood washed off under cold running water. Next, suitable bits were macerated and finely divided for 1½–2 minutes in an Ato-mix (blender) with a solution of 0.9 % NaCl. For a whole brain, 1½–2 litres NaCl solution warmed to about 40° C were used. The emulsion stood for 1–2 hours after which it was centrifuged for at least 15 mins. at 2,500 r. p. m. The extract was then decanted and the deposit thrown away.

The activity of the thromboplastin was tested in the following way: Parts of the extract were diluted (1 : 1, 1 : 2, and 1 : 3) with physiological saline and the prothrombin complex time of normal plasma was estimated using Quick's method (0.2 ml brain extract + 0.2 ml normal plasma were mixed in a test tube, put in a water bath at 37° C and then recalcified with 0.2 ml 25 mM $CaCl_2$ solution at the same temperature). Depending on the results of this test, all the extract was diluted to the lowest concentration which gave optimal activity. During the final dilution, Owren's buffer corresponding to 10 % of the whole extract was added as well as physiological saline. The final extract was put in small tubes in amounts needed for daily use and stored at –20° C.

Prothrombin free and proconvertin free ox plasma.

Ox blood (9 volumes) was bled straight into 1 volume 2.5 % (w/v) potassium oxalate (monohydrate) and mixed at once. The oxalated blood was centrifuged at 2,500 r.p.m. for about 15 mins. The plasma was then pressure filtered through a clarifying filter containing 20 % asbestos and then twice through a filter containing 30 % asbestos. (If a filter containing 50 % asbestos, instead of 30 %, is used after the initial clarifying filtration, one filtration will usually be sufficient.)

The following test was carried out to make certain that the plasma no longer contained prothrombin or proconvertin after filtration: 0.2 ml ox plasma + 0.2 ml thromboplastin were mixed in a test tube, placed in a water bath at 37° C and then recalcified with $CaCl_2$ solution (about 35 mM) (see later). If the coagulation factors mentioned were absent, the mixture would not coagulate. If it did coagulate, the plasma was re-filtered through the 30 % asbestos filter. In practice it was stipulated that the mixture should stand for at least 20 mins. without coagulating. By adding 0.5 N HCl, the plasma pH was adjusted to 7.35 with a glass electrode. When ready, the plasma was put in small tubes in the approximate amounts needed for daily use and stored at –20° C.

Owren's buffer

has the following composition:

Sodium-diethylbarbiturate	11.75 g
NaCl	14.67 g
HCl, 0.1 N	430 ml
Distilled water to	2,000 ml

The pH was controlled and adjusted to 7.35 with a glass electrode.

The plasma dilution fluid

has the following composition:

Potassium oxalate (monohydrate) 0.7 %	100 ml
Owren's buffer	200 ml
NaCl 0.9 % to	2,000 ml

Original $CaCl_2$ solution.

About 100 g calcium chloratum sicc. pro analysi was dissolved in 1,000 ml distilled water. The concentration of calcium was determined by estimating the concentration of chloride. The solution was then diluted to *500 mM*.

$CaCl_2$ solution for optimal recalcification.

The calcium chloride concentration for optimal recalcification was determined experimentally for each new supply of ox plasma. The method was as follows: the original solution of 500 mM $CaCl_2$ was diluted to 50 mM with distilled water. By further dilution with Owren's buffer, calcium chloride solutions of 20, 25, 30, 35, 40, 45 and 50 mM were made. Each of these were tested (double tested) against a normal plasma in Owren's system (see below). The optimal calcium chloride concentration is that which gives the shortest coagulation time in the system, and this was used for the ox plasma. A solution containing 35 mM $CaCl_2$ was usually the optimal one.

Practical technique in estimation of PP values.

4.5 ml blood was aspirated by venepuncture into 0.5 ml 2 % (w/v) potassium oxalate (monohydrate) in a 5 ml record syringe and mixed immediately. The oxalated blood was then centrifuged and 0.2 ml plasma was diluted with 1.8 ml plasma diluting fluid. The concentration of oxalate in the diluted plasma was 100 mg %.

0.2 ml of the prothrombin and proconvertin free ox plasma were mixed in a small serological test tube with 0.2 ml thromboplastin and 0.2 ml of the diluted plasma. The mixture was put in a water bath at 37° C for 5 mins. It was then recalcified with 0.2 ml of the optimal $CaCl_2$ solution, and the coagulation time found in the usual way with a stop watch.

The coagulation time in this system depends on the combined effect of prothrombin and proconvertin in the plasma investigated. It was expressed as a percentage of the normal with the help of a correlation curve. The curve was made as described by *Owren* (1949), by estimating the coagulation time of increasing dilutions of normal plasma. These dilutions were made of the normal 10 % dilution by using a diluting fluid like that given above but with 100 mg % potassium oxalate (instead of 70 mg %) to obtain a constant concentration of oxalate in all dilutions. On double logarithmic paper, with the dilutions expressed as percentages as the abscissa, and the time in seconds as the ordinate, the correlation curve approaches a straight line. The standard solution (10 %) of normal plasma represents 100 %. The PP value of the plasma investigated is read off as a percentage of the normal value.

The normal standard was determined as the average of 10–20 normal blood samples and was controlled at intervals to make certain that the value remained constant. When a new correlation curve was introduced (a new one must always be made before starting to use a new supply of ox plasma or new thromboplastin extract), it was made certain that the values in the old and new coagulation systems corresponded accurately by comparing a number of samples in the two systems. Frozen standard plasma was also occasionally used as control to make even more certain that there were no changes in values, especially when changing to a new correlation curve.

All the PP values in the present investigation were double tested.

The samples of blood were investigated immediately after they were taken (the only exceptions being a few samples from 4 patients when they were away on business or holiday). Neither addition of a small amount of heparin (to stop activation of proconvertin) nor mercaptol (to prevent damage by bacteria), as recently recommended by *Owren* (1954), was therefore considered necessary (see p. 29).

Serum cholesterol estimation.

The total serum cholesterol was estimated as described by *Kingsley and Shaffert* (1949) without saponification. As is known, cholesterol esters give a stronger colour in the Lieberman Burchardt reaction than free cholesterol. This is corrected for by multiplying the values found by the factor 0.84.

Liver function tests.

In order to see whether prolonged use of dicoumarol had any demonstrable effect on the liver function, the following tests were carried out on all the patients in the treated group:

Icterus index (Meulengracht).

Thymol turbidity test (Maclagan 1944).

Gros' test as modified by Stolte *(Gros* 1939, *Christoffersen and Raagaard* 1947).

Fractional estimation of *serum albumin and serum globulin (Howe* 1921).

Electrocardiographic technique.

The technique for taking electrocardiograms used in the three medical departments during the investigation was registration of the 3 standard extremity leads and IV F. If, however, myocardial infarction was suspected, these were supplemented by the praecordial leads IV R and CF_2. Frequent electrocardiograms in the first and second week after an acute attack were considered especially important, partly because the gradual changes during the course of the disease could thus be followed, and partly so that the relatively late changes which may confirm the diagnosis of an infarct after an acute attack of praecordial pain would not be missed. Unipolar leads were only used exceptionally.

Radiological examination of the heart.

Radiological examination of the heart was, in all the patients in this investigation, carried out using *Jonsell's* modification (1939) of *Liljestrand, Lysholm, Nylin, and Zachrisson's* method (1939) which is based on Rohrer–Kahlstorf's formula for determining the cardiac volume. See *Rohrer* (1916) and *Kahlstorf* (1932). The examinations were performed in the Roentgen Department in Ullevål Hospital (Head, Dr. J. Frimann-Dahl M. D.). All the X-rays were examined and measured by Dr. Per Amundsen. *Amundsen* (1956) has shown that the errors in radiological estimation of the heart volume are considerably reduced if the measurements are all made by the same trained observer. The reader is referred to the same author for more details of the radiological technique.

Summary and conclusion.

The following subjects have been discussed in this chapter: (1) Allotting patients to treated and control groups. (2) Clinical investigation of the patients while in hospital. (3) Criteria for the diagnosis of the acute infarct. (4) Special investigations used (laboratory techniques, electrocardiograms and radiological examination of the heart).

It has been shown that neither the author, the doctors referring the cases nor anyone else who might have a subjective point of view, have had an opportunity of influencing the distribution of the patients between the two groups to be compared. An exception from this was, however, the patients in the treated group in whom, for different reasons, long term therapy was impossible, and the corresponding patients in the control group, all of whom had to be excluded from the investigation. This exclusion was done by the author, usually in consultation with other doctors, and, according to uniform principles which had been previously laid down. Subjective selection was thus prevented.

The final result of allotting the patients to the treated and control groups will be illustrated and discussed in connection with the statistical comparison of the

two groups which was considered as a necessary background for evaluating the results. The excluded patients will also be discussed in more detail later.

The possibility of using placebos in the control group was considered, but rejected for ethical and legal reasons.

Details are given of the schedule drawn up for the clinical investigations while in hospital and the measures taken to ensure that all the patients had as similar investigations as possible.

Finally, the most important special investigation techniques are mentioned, and more details are given of the method for determination of prothrombin-proconvertin, Owren's PP method, which plays an important part in this investigation.

CHAPTER V

Selection of patients for the investigation.

The total material—section A.

The raw material for this investigation (designated section A) consisted of 277 consecutive patients treated for acute myocardial infarction in Ullevål Hospital Departments VII, VIII, and IX in the period July 1950 to July 1953. They were all under 76 years old on admission.

According to plan, the use of anticoagulants in the control group should be discontinued after a maximum of 1 month, this therefore marks the beginning of the true observation time for the controlled therapeutic trial. No patient was therefore included in this investigation (either in the control or treated group) unless he survived for the first month of treatment + the period from the acute attack to the commencement of treatment. It was also stipulated that the latter period should not exceed 1 month. It can therefore be stated that the 277 patients who provided the raw material for this investigation had all survived their acute infarcts by between 1 and 2 months when the observation time started. Further details concerning the interval between the acute infarct and admission to hospital are shown in Table 19 page 70.

Of the 277 patients in section A, 138 were assigned to the treated and 139 to the control group. The principles followed for inclusion in one or other group are referred to in Chapter IV.*

The inclusion of patients in the investigation was originally stopped on the first of April 1953, when there were 261 patients. However, in the period from the middle of May to the middle of July 1953, 16 additional cases were included. The reason was that, in the daily press, a great deal of publicity was given to the question of long term treatment with anticoagulants in cardiovascular disease. One therefore had to reckon with the possibility that many of the patients in the control group would desire this form of treatment and possibly deplete the control group. Even if this did not happen it would be an advantage to have a larger number of cases in the investigation.

* The only exception from this was the selection of the first 10 patients who were all admitted to Dept. VIII where the investigation was first started. These were divided between the treated and control group by allotting patients to different groups on odd and even dates of admission.

These last 16 cases consisted of 7 consecutive patients from Dept. VIII who were included in the treated group and 9 consecutive patients from Dept. IX who were included in the control group.*

Patients excluded from the controlled clinical trial according to plan.

As mentioned earlier, it was reckoned that some of the patients originally included would not be able to carry through the regime necessary in ambulant anticoagulant therapy. See page 47.

Of the 138 patients in the treated group there were 6 men and 6 women who were not able to undergo this form of treatment and who therefore had to be excluded from the investigation.

TABLE 4.

Patients who had to be excluded from the treated group because they could not have undergone long term ambulant treatment with anticoagulants, and those excluded from the control group because they could not have undergone such treatment had they been in the treated group.

Reason for exclusion	No. of patients Treated group	Control group
I. Severe heart failure	1	2
II. Immobilising disease of skeletal muscle or nervous system		
(1) Chronic rheumatoid arthritis	1	1
(2) Advanced arthrosis of hip and spine	1	1
(3) Hemiparesis after cerebral accident		1
III. Mental diseases or severe psychic debility		
(1) Acute psychosis	1	
(2) Depressive psychosis, transf. to psy. dept.	1	
(3) Mental defective	1	
(4) Senile dementia (cerebral arterioscl.)	1	
IV. General physical and psychic deterioration because of age and arteriosclerosis—combined with heart failure and/or angina pectoris	1	4
V. Serious complicating condition with bad prognosis (anticoagulants possibly contraindicated)		
(1) Pulmonary tuberculosis with cavitation		1
(2) Renal tuberculosis with cavitation		1
(3) Renal disease with uraemia + advanced aortic valvular disease (luetic)		1
(4) Diabetes mellitus with advanced nephropathy and retinopathy + polycythaemia vera		1
VI. Geographical conditions		
(1) Living in another part of the country	3	
(2) Living abroad	1	1
Total number of patients who had to be excluded at the outset	12	14

* These last patients in the control group were all from Dept. IX because the doctors in Dept. VII had started long term treatment in some cases of infarct in April 1953.

Of the 139 patients in the control group there were 6 men and 8 women who would not have been able to undergo continuous ambulant treatment with dicoumarol if they had been in the treated group. They therefore also had to be excluded.

The reasons for these patients being excluded are shown in *Table 4* and it is clear that in all cases these reasons were very weighty. In fact it was only insurmountable obstacles that were accepted as reasons for exclusion.

It is stated in many publications on long term treatment with anticoagulants that "only intelligent and co-operative patients were chosen for this form of treatment". No such selection was made here. It was thought first of all that such a selection could bias the investigation and reduce its dependability. Secondly, it was considered that the amount of intelligence required can be reduced to a minimum if the technique at the follow-up clinics and the dose regulation is given careful consideration. On the basis of personal experience, it was also thought that the necessary regime provides opportunities for supervision and for influencing and increasing the patient's co-operation.

After exclusion of the patients mentioned above, the group of patients for the controlled clinical trial was reduced from 277 to 251, of which 126 were in the treated and 125 in the control group.

Additional patients excluded from the controlled clinical trial.

The group of patients for the controlled investigation was, however, further reduced for different reasons outside the influence of the investigator.

Of the 126 patients after primary exclusion in the *treated group,* there were 7 cases (3 men and 4 women) who were also eliminated from continued treatment with anticoagulants. The reasons for this are shown in *Table 5.* It will be seen that in 4 of these 7 cases the reason was that the patient himself did not want continued treatment and supervision after discharge, and in 1 case it was because of progressive dementia leading to an inability to keep to the dosage prescribed so that the control became illusory. In only 2 cases was treatment stopped as a result of haemorrhagic conditions and established contra-indication to continued treatment with anticoagulants. One of these cases was a 66 year old man in whom, after 3 months ambulant treatment, anaemia and blood in the stools were demonstrated. The bleeding continued after the PP value had become normal. As thorough clinical and radiological investigation were not able to demonstrate the primary cause of the bleeding, an exploratory laparotomy was carried out, which showed haemangiomatosis in the mid part of the small intestine for a length of about ½ metre. Resection was not performed, and continued treatment with anticoagulants was considered to be contra-indicated. The other case was a 60 year old man with essential hypertension (B P 230/100–240/115) and signs of advanced arteriosclerosis. After 12½ months treatment with satisfactory control he deve-

TABLE 5.

Patients who had to be excluded from the *treated group* because of obstacles to the execution or completion of the treatment planned.

Reason for exclusion	No. of patients
I. Did not wish continuous treatment with anticoagulants	
(1) Refused venepuncture while in ward, took own discharge	1
(2) Did not wish treatment with anticoag. after discharge	1
(3) Broke off amb. tr. after 2 months	1
(4) Neurosis, after 3 months wanted to go back to previous doctor for treatment	1
II. Progressive dementia, did not succeed in keeping to dosage. Treatment stopped after 9 months—unsatisfactory control	1
III. Haemorrhagic conditions. Established contra-indications for continued treatment.	
(1) After 3 months amb. tr.—anaemia and occult bleeding. Laparotomy: intestinal haemangiomatosis	1
(2) Severe essential hypertension. After 12 months amb. tr. cerebral haemorrhage with transitory left hemiparesis (PP value 37 %)	1
Total number of patients	7

loped a cerebral haemorrhage with transitory left sided hemiparesis. The PP value estimated 3 hours after the onset was 37 %. It was considered that his hypertension and arteriosclerosis were the primary causes, and the use of anticoagulants a contributory cause of bleeding. Continued treatment was considered to be contra-indicated.

Of the 125 patients after primary exclusion in the *control group* there were 7 cases (4 men and 3 women) who had to be eliminated as they later fell below the standard for patients in the control group. The reasons for this are shown in *Table 6*. It will be seen that 1 patient was difficult, refused treatment especially venepuncture and took her own discharge. It would have been impossible to give

TABLE 6.

Patients who had to be excluded from the *control group* either because long term anticoagulant therapy was started or because they would have been excluded had they been in the treated group (1 case).

Reason for exclusion	No. of patients
I. Refused venepuncture while in ward, took own discharge	1
II. Treatment with anticoagulants started	
(1) By the investigator by special request	1
(2) By other doctors or hospitals	5
Total number of patients	7

her continued anticoagulant therapy, and she therefore had to be excluded although she was in the control group. Five patients had to be excluded because

continuous anticoagulant therapy was subsequently started by doctors in other hospitals. In 1 patient, who was a doctor employed in the hospital, treatment with anticoagulants was continued by the investigator by special request.

On account of the above-mentioned "secondary" reasons for exclusion the group of patients for the investigation was reduced further from 251 to 237 cases, of which there were 119 in the treated and 118 in the control group. These patients provided the basis for the controlled clinical trial and has been termed *section B*.

Summary.

In this chapter the size of the raw material—section A—has been reported on. The patients included were all under 76 years old, they were admitted to one of the three medical departments and had survived a definite episode of acute infarction. Next, the number of patients in each group is mentioned who, according to the plan of the investigation, had to be excluded either because they were not able to undergo the necessary out-patient control and treatment, or for other reasons. Finally, a very few patients had to be excluded because, for reasons outside the influence of the investigator, they did not satisfy the requirements for the investigation. Section A consisted of 277 cases and it was thus reduced, forming section B, to 237 cases, 119 in the treated group and 118 in the control group. These cases formed the basis for the controlled clinical trial.

CHAPTER XVIII

Discussion and conclusion.

The controlled clinical trial, of which a full account has been given in the previous chapters, shows that correctly managed long term treatment with dicoumarol of patients *under 60 years old* has resulted in a statistically significant reduction both in the incidence of recurrent infarction and in the mortality *during the first 12 months* after an acute infarct.

The presumption that this statistical significance does not depend on chance is supported by making a comparison of many other factors in the treated and control groups, all of which are in favour of the treated group: (1) The incidence of recurrent infarction and the mortality in patients over 60 years during the first 12 months are also considerably lower in the treated than in the control group, but the difference is not statistically significant. (2) Attacks of severe retrosternal pain in which the presence of a recurrent infarction was suspected but not verified were observed about half as frequently in the treated group as in the control group. (3) The morbidity from cardiovascular disease, judged by the frequency and duration of admissions to hospital during the observation period is considerably lower in the treated than in the control group. (4) Severe heart failure develops less often in treated than in untreated patients. (5) The electrocardiogram more often returns to normal after the recorded infarct in the treated than in the control group. (6) The incidence of thrombosis in a coronary artery shown at autopsy is significantly lower in the treated than in the control group, but it should be remembered that the proved comparability of the two groups probably does not hold good for the post mortem cases in each group.

The greatest difference between treated and untreated cases, and the only difference which is statistically significant with the level used (5 %) is thus in the incidence of recurrent infarction and the deaths in patients *under 60 years old* and *during the first 12 months.* These two points will now be examined in more detail.

Age factor: It might at first seem surprising that the treatment had most effect in the younger age groups. The number of observations (recurrent infarcts, deaths) is certainly considerably larger among the oldest cases, so that this group should numerically be the best for showing the effect of treatment. All the same, it is among the younger cases (under 60 years) that the difference is statistically significant.

Previous studies of the prognosis have shown that the mortality ratio after myocardial infarction is considerably higher in relatively young than in older

patients. This is shown especially clearly in *Westlund and Hougen's* investigation from Oslo (1956) (see also p. 25). They found that "the mortality ratio (ratio between actual and expected number of deaths) in the first year after discharge varied from 15.5 at ages 40–49 to 4.8 at ages 80–89". The mortality ratio which can be counteracted by treatment is thus considerably higher among the younger age groups.

Although, as far as the author is aware, it has not been especially investigated or proved, it is reasonable to assume that *thrombosis* is relatively more important in the aetiology of coronary occlusion and in the deaths from coronary disease in the younger than in the older age groups. It is therefore not unreasonable after all that one achieves less with long term anticoagulant therapy in older patients who probably more often have advanced coronary *sclerosis* and a more damaged myocardium than younger patients.

It should perhaps be pointed out here that the incidence of recurrent infarction and the mortality were high and there was no special difference between the treated and control groups in the group of patients in this investigation who had had more than one infarct before the beginning of the observation period. Although this group of patients was small, the results seem to indicate that the effect of treatment is slight or uncertain in patients with recurrent infarction. It was also found that the effect of the treatment seems to be better in patients with normal cardiac volume than in those with an enlarged heart.

Together with the demonstration of the definite effect in the younger age groups, this finding is of considerable practical interest. It is in contrast with previously predominant ideas of the indications for treatment which are usually based chiefly on theoretical considerations. Thus, in 1944 when *Nichol* introduced this treatment into cardiology, it was for patients with a tendency to recurrent infarction *(Nichol and Fasset, 1947)*. Since then, Nichol and his co-workers have used this treatment in coronary disease with many different indications including cases of impending infarction (see p. 36 and *Nichol,* 1950). *Wright and co-workers* (see pp. 33–34) maintain that long term anticoagulant therapy is indicated in *recurrent* myocardial infarction, especially if there are thromboembolic complications or if periods of heart failure are a predominant feature. *Suzman, Ruskin, and Goldberg* (1954) are of a similar opinion on the basis of their investigation (see pp. 37–38). "Patients in whom the presenting attack is mild in addition to being the first one, and who receive short-term anticoagulant therapy, show a favourable 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."

On the other hand, *Waaler* (1956) has found, after a thorough study of angina pectoris patients with long term therapy from Owren's material, that there is a

statistically significantly lower mortality among patients in whom treatment is started within a year of diagnosis. (See also p. 35.) *Olsen, Kahrs, Rømcke, and Lingjærde* (1956) have investigated the long term prognosis among untreated infarction patients who were divided in retrospect into "good risks" and "poor risks". They found that the patients in the "good risk" group more often died of new infarcts whereas patients in the "poor risk" group more often died of heart failure. They maintain that there is thus a theoretical basis for giving long term anticoagulant therapy primarily to the "good risks".

Owren (1955) strongly emphasises that long term anticoagulant treatment is prophylactic and not curative. The results of the present controlled investigation support this opinion: in old patients and those with multiple previous infarcts where there must be assumed to be extensive and irreparable damage of the coronary circulation and of the myocardium, the treatment seems to be of little value. The most definite and greatest effect was in the younger patients who had only had one previous infarct. Paradoxically, it can perhaps be said that whereas short term treatment in acute myocardial infarction is primarily indicated in "poor risks", long term therapy is primarily indicated in "good risks".

Time factor: In patients under 60 years old, *a definite effect of treatment can only be demonstrated during the first 12 months,* as mentioned previously. Later on there is no obvious difference between the treated and control groups. The limit of 12 months was chosen arbitrarily. The figures seem to indicate that the difference was greatest in the first 6 months.

Most of the earlier prognosis studies show that the first year after an acute infarct is more dangerous and the mortality ratio is higher than in subsequent periods. This is especially well illustrated by *Westlund and Hougen* (1956) (see also page 25). They found that "the mortality ratio (ratio between actual and expected number of deaths) among males 60–69 years old varied from 8.1 in the first year after discharge to 2.1 ten years and over". It therefore seems reasonable that the treatment should achieve most in the first period in which the mortality ratio and also the incidence of new or extended coronary thrombosis and recurrent infarction are highest. It is also primarily in this period that collateral vessels develop and possibly also recanalisation occurs which are so important for the prognosis.

On the other hand, it is also clear that, even though in this study no difference was found between the treated and untreated cases after the first year, the possibility has not been excluded that the treatment *could* have a definite effect for a longer period. During the first year, selection of the material took place as more of the worse cases died in the control than in the treated group. A bias thus arose in disfavour of the treatment and this might have prevented recognition of the possible development of a real difference. It is impossible to state how large a part this has played in this investigation. In order to assess the effect of treatment definitely, for instance in the period from 12–24 months after an acute infarct,

patients should be investigated who had *all* been treated (or not treated) for the whole of the first 12 months. Subsequently, for example by drawing lots, this material should be assigned to a treated and an "untreated" (or placebo treated) group which would then be observed for the following 12 months.

In the author's opinion, future controlled clinical trials of the effect of long term anticoagulant therapy should aim at assessing the effect over a limited period. This would greatly simplify the problems and have many practical and statistical advantages.

In this study, the results were achieved after treatment with dicoumarol which was both consistent and intensive (see Chapter IX). The treatment was, at any rate, considerably more intensive than that in the few previous investigations in which such information is given. In the author's opinion there is no reason to believe that one could achieve better results with this form of anticoagulant therapy. This is confirmed by the fact that cases of recurrent infarction and sudden death in the treated group, with very few exceptions, occurred when the treatment was adequate and the PP values were low (see Chapter XII). They were therefore not caused by a relative reduction in the intensity of treatment.

In spite of this intensive treatment, haemorrhagic complications were not a serious problem (see Chapter XIII). The incidence of haemorrhages was no larger than that in the large investigations previously published by experts. It is worthy of note that the incidence of severe cerebral vascular accidents was similar in the control group and in the treated group, although, as would be expected, the mortality from this condition was higher in the treated group.

This study has thus shown that long term treatment with dicoumarol after acute myocardial infarction has a definite effect, but that this effect has marked limitations. Treatment is far from providing absolute prophylaxis for recurrent infarction and sudden cardiac death. This is not surprising seen in the light of the theoretical considerations in Chapter II, and in the knowledge that thrombosis seems to be the cause of coronary occlusion and of death from coronary disease in only 50 % of cases. In this investigation as a whole, treatment during the observation period has resulted in a reduction in the incidence of recurrent infarction by about 45 % and in the mortality from cardiovascular diseases by about 37 %. When it is remembered that treatment with dicoumarol has no absolute antithrombotic effect, these results seem to be theoretically reasonable. In this study, thromboembolic complications other than coronary thrombosis seem to be very infrequent in myocardial infarction after the acute phase, and they are therefore not an indication for long term treatment. Exceptions to this appear to be only the cases in whom, besides coronary disease, there are signs of peripheral obliterating arteriosclerosis with the possibility of secondary thrombosis.

The limited effect of the treatment is demonstrated most clearly by the fact, previously mentioned, that a statistically significant effect was only shown in

patients under 60 years old during the first 12 months of the observation period. The age-limit (60 years) and the limit of duration (12 months) have been chosen arbitrarily. Thus, as mentioned, it has not been proved that long term dicoumarol therapy in older patients and for longer periods is ineffective. There are in this investigation different observations which seem to indicate that the opposite may be true. There is, however, a very clear *difference in the grade of effect* between younger and older patients and between the first 6–12 months and later periods. This *quantitative difference* is of great practical significance when considering the indications for treatment.

The effect of treatment shown in this investigation is, in the opinion of the author, not such that it justifies long term treatment throughout life of *all* patients with myocardial infarction, with the enormous consequences this would have. It would usually be both practically and economically impossible. It seems, on the contrary, that the indications for this form of treatment should be different and stricter than those previously employed. The results of the controlled clinical trial give reason to believe that the energy available in medical departments, laboratories and among specialists would be most profitably expended on relatively young patients who have only had one infarct. Thus, far more would probably be achieved by treating all or a large number of these patients for, for example 6 months or a year, than by treating a smaller unselected number of infarction patients for the rest of their lives.

General summary.

The object of this study has been to investigate the prophylactic value of long term treatment with dicoumarol after acute myocardial infarction.

In *Chapter I* the background to the study is mentioned. A short account is given of the discovery of dicoumarol, its introduction into clinical medicine and the results of anticoagulant therapy in acute myocardial infarction.

In *Chapter II* the problem of the investigation is presented. This is followed by an account of the theoretical and practical considerations for the solution of the problem. On the basis of the literature, the most important factors in the *pathogenesis of coronary occlusion* are discussed with special reference to the significance of thrombosis as the cause of the occlusion. Previous investigations indicate that thrombosis is only the cause of coronary occlusion in about 50 % of the cases. This gives a theoretical limitation of the prophylactic value of anticoagulant therapy. Details are also given of the possibility that thrombosis may be a contributory cause of atherosclerosis, as has been recently maintained by some investigators especially Duguid.

Bearing in mind the question of whether or not the problem of the investigation can be solved within a reasonable time, an account is then given of previous experiences of the *prognosis after acute myocardial infarction.* The prognosis varies markedly in different publications. The reasons for this are discussed briefly. On the whole, however, the prognosis is bad enough for the possible effect of prophylactic therapy to be evident within a few years.

In the last section of this chapter, it is shown that there were good opportunities for collecting a sufficiently large number of patients who would be able to be under continued supervision. Further, an account is given of the theoretical background for Owren's PP method of prothrombin and proconvertin estimation, which, in this study, is the basis for control of the antithrombotic effect during treatment.

In *Chapter III* a brief account is given of the previous publications on long term anticoagulant therapy. It is evident that the main aims of most previous publications have been to show firstly that treatment of ambulant patients is practicable, and secondly how it should be carried out. Only a few articles have attempted to demonstrate the effect of treatment, and satisfactorily planned and controlled clinical trials have not been published. If the technique of control of dosage is satisfactory, haemorrhagic complications are not a very great problem.

At any rate, they give no reason for rejecting the treatment. There is a great need for controlled investigations which are able to clarify the effect of and indications for treatment.

In *Chapter IV* more details are given of the plans for the investigation, especially the method chosen for allotting patients to treated and control groups. It is shown that neither the investigator, the doctor referring the case nor anyone else who might have a subjective point of view have influenced the assignment of patients to the groups. The only exceptions to this were a few patients who had to be excluded because they could not attend out-patient clinics. The principles for this exclusion were uniform in the treated and control groups.

Details are also given of the lines followed in the clinical investigation of the patients in hospital, and of the precautions taken to ensure that all the patients had as similar investigations as possible. Finally, an account is given of some special investigation techniques, especially the method for estimation of prothrombin and proconvertin, Owren's PP method, which plays an important part in this investigation.

In *Chapter V* the material is discussed. In all, the raw material consisted of 277 consecutive patients. They were all under 76 years old and had survived an acute myocardial infarct by a minimum of one month (30 days) and a maximum of two months. Next, the number of patients in each group is mentioned that had to be excluded from the investigation as, on account of illness, geographic conditions or for other reasons, they were not able to attend the necessary out-patient clinics for supervision and treatment. A few additional patients had to be excluded as, for reasons outside the influence of the investigator, they did not satisfy the requirements for the clinical trial. The original material, consisting of 277 cases and termed "section A", was thus reduced to 237 cases (119 treated and 118 control) which formed the basis for the controlled clinical trial and was termed "section B".

In *Chapter VI* a detailed analysis and statistical comparison of the treated and control groups is given in order to show the comparability of the two groups at the beginning of the investigation. This comparison was made both for section A and for section B. This was done in order to find out whether the exclusion of patients had biased the comparability in any way. The statistical comparison was made for many different criteria which fall into 3 main groups: I. General characteristics. II. Facts in the past history thought to have significance for the prognosis. III. Course of the recorded infarct.

Apart from a couple of differences caused by errors in investigation technique, there was no significant difference with the 5 % level of statistical significance between the treated and control groups either in section A or section B. In all, the statistical comparison of the treated and control groups provides *a good basis for stating that the patients were allotted by chance to the two groups.*

In *Chapter VII* an account is given of the treatment in hospital during the

acute phase of the infarct. The conditions governing the medical care, nursing and general care were uniform for all the patients, and in this respect there was no difference between the treated and control groups. An analysis of the main cardiological treatment also showed very uniform conditions in the two groups.

All the patients in both groups had anticoagulant treatment with dicoumarol during the first month and this treatment was supervised and the doses prescribed by the author in all cases. There is therefore no evidence for any differences in the administration of dicoumarol. Both thromboembolic and haemorrhagic complications occurred infrequently during the acute phase and their distribution was almost exactly the same in the treated and control groups. There was no evidence that the treatment in hospital during the acute phase of the infarct had biased the comparability of the groups thus influencing the subsequent comparison.

In *Chapter VIII* an account is given of the lines followed in the observation and treatment of patients in the ambulant phase. All the patients in both groups had regular cardiological supervision by the author. Great efforts were made to give the patients in the control group as thorough supervision and treatment, apart from the use of dicoumarol, as the patients in the treated group. An account is given of the general lines followed for dosage and control of dicoumarol therapy. Finally, it is shown that the length of the observation period is completely comparable in the treated and control groups and that collection of the material has taken place over exactly the same period (3 years).

In *Chapter IX* an account is given of the intensity of the anticoagulant therapy as judged by the PP values recorded during the observation period. Such information is of great significance and interest but is only given exceptionally in previous publications. It was calculated that the PP value was under 30 % (i. e. 29 % or less) for 82.5 % of the period of treatment and under 40 % for 92.3 % of the period. The value was in the range 10–19 % for about 46 % of the period. The intensity of the treatment was also calculated in each individual patient. It was shown that the PP value was under 30 % for 70–100 % of the period of treatment in 103 of the 119 patients. In comparison with the information from other investigations, this treatment must be considered to be very intensive and effective, and it is reckoned that the antithrombotic effect of dicoumarol has been used to the full. In the control group, anticoagulant therapy was only given as short term treatment of recurrent infarction and of a few other thromboembolic episodes.

In *Chapter X* recurrent infarction during the observation period in the treated and control groups is discussed. Details are given of the method of diagnosis and of the criteria for the different grades of diagnostic certainty. Next, an account is given of the incidence of recurrent infarction in relation to sex and age. A thorough statistical investigation is also made of the "force of recurrence", i.e. the probability per unit of time at a given point of time in the observation period that recurrent infarction will occur. This investigation shows that *with 5 % level,*

the force of recurrence for patients under 60 years old is significantly higher in the control than in the treated group during the first 12 months of the observation period. The difference in patients over 60 years has the same trend but is not statistically significant. After 12 months there is no definite difference between the groups, either over or under 60. There is evidence that the force of recurrence was especially high in patients who had had several previous infarcts, and that treatment of such cases may have least prophylactic effect. It has also been shown that the force of recurrence increases with increasing cardiac volume.

In *Chapter XI* the mortality during the observation period is discussed. An account is given of the information received about the deaths and the causes of death. The relation of mortality to both age and sex is given. Next, a thorough statistical investigation is made of the "force of mortality" i.e. the probability per unit of time at a given point of time in the observation period that death will occur. This showed that *with 5 % level, the force of mortality in patients under 60 years is significantly higher in the control than in the treated group during the first 12 months of the observation period.* The difference in patients of 60 years and over during the same period is not statistically significant. After 12 months there is no certain difference between the groups either over or under 60. The investigation also shows that the mortality is relatively high in patients who have had several previous infarcts, and it appears that treatment is not especially indicated in such cases, as has previously been assumed. The mortality also increases with increasing cardiac volume and anticoagulant therapy seems to have more effect in patients with a normal sized than in those with an enlarged heart.

In *Chapter XII* a detailed account is given of the PP level both in the weeks preceeding, and in direct relation to the 26 recurrent infarcts and 5 cases of sudden death that occurred in the treated group. It is shown that a relative reduction of the intensity of the treatment cannot have played an important part in causing these episodes. Most of them occurred while the PP level was under 30 %.

In *Chapter XIII* an account is given of the number, type and degree of severity of the haemorrhagic complications during treatment with dicoumarol. In all, one haemorrhagic episode was observed every 7.9 years of treatment per patient and one moderate or severe haemorrhage every 13.1 years of treatment per patient. In spite of the intensity of the treatment, the incidence of haemorrhage is no higher than that observed in previous large investigations by experts. About half the haemorrhagic episodes occurred while the PP value was under 10 % and in the other half the PP value was between 10 and 34 %. In a good ⅓ of the cases contributory local causes apart from anticoagulant therapy were found. Four cases of cerebral haemorrhage occurred all of which were fatal. However, in the control group there were also 5 severe cerebral vascular accidents one of which was fatal and 3 of the others resulted in permanent invaliding hemiparesis. Apart

from these cases, there were only 4 cases of moderate haemorrhage during the observation period in the control group.

In *Chapter XIV* an account is given of the tests carried out to investigate the liver function during the long term treatment with dicoumarol. With the tests used, no sign of liver damage was demonstrated apart from 4 cases in which the thymol turbidity test became positive during the treatment period for unknown reasons.

In *Chapter XV* details are given of the patients' mode of life, ability to work and morbidity during the observation period. No important difference was shown between the groups with regard to mode of life, ability to work and type of work. However, the incidence was higher and the duration of admissions to hospital longer for cardiovascular disease during the observation period for patients in the control than in the treated group. There was, however, no difference between the groups in morbidity from intercurrent diseases. Severe heart failure was observed in 3 times as many patients in the control group as in the treated group, 12 and 4 cases respectively. A detailed investigation was not made into the prophylactic effect of treatment against attacks of angina pectoris, but a rough comparison was made for the two groups and showed no convincing difference. The number of cases with increase in size of the heart (estimated radiologically) was also about equal in the two groups. A lasting return to normal of the electrocardiogram after the recorded infarct was observed in 28 patients in the treated group and 17 in the control group. Intermittent claudication developed during the observation period in 8 patients in the control group and only 1 in the treated group who had not previously had this symptom. Other extra-cardiac thromboembolic complications in the control group included only one case of thrombophebitis and one case of pulmonary embolism.

In *Chapter XVI* the medical and psychological significance of regular supervision of patients after myocardial infarction is discussed briefly, and the need for such supervision is emphasised.

In *Chapter XVII* details are given of the autopsies carried out in 43 of the 66 cases who died during the observation period. The presence of the originally diagnosed acute infarct was verified in all the post mortem cases. Both coronary thrombosis and other thromboembolic phenomena were shown at autopsy 2–3 times as frequently in the control as in the treated group. The incidence of coronary thrombosis was significantly higher in the control than in the treated group, but it should be remembered that the proved comparability of the two groups probably does not hold good for the post mortem cases in each group. The results indicate that long term treatment with dicoumarol does have an anti-thrombotic effect on the development of coronary thrombosis, but, at the same time, it does not provide complete prophylaxis. On the whole, the autopsy findings support the previously mentioned investigations into the clinical effect. The weight of the heart was increased in relation to the average standard values

in all the post mortem cases. In most cases the increase in weight was considerable.

In *Chapter XVIII* there is a brief discussion of the results of the controlled clinical trial. Besides the statistically proved difference in the forces of recurrence and of mortality in patients under 60 years old and in the first 12 months, the effect of treatment is substantiated by many other observations most of which have been mentioned earlier in this summary. The influence of the age factor and the time factor on the effect of treatment is discussed in more detail. It is emphasised that the effect is greatest in the first 6–12 months after the acute infarct. It is further pointed out that the results of this investigation seem to be theoretically reasonable in the light of previous pathological observations and studies of the long term prognosis after acute myocardial infarction. Although the view usually held previously has been that treatment is especially indicated in patients with recurrent infarction and the worse cases after severe infarction with a tendency to heart failure and thromboembolic episodes, this investigation has shown that it is primarily the younger patients and those who have only had one infarct who benefit from this form of treatment. This is reasonable when it is remembered that the treatment is primarily prophylactic and not curative. Paradoxically, it can therefore perhaps be said that while short term treatment of acute myocardial infarction is primarily indicated in the so-called "poor risk" cases, long term therapy is primarily indicated in the "good risk" cases.