1960

Long term anticoagulant therapy following myocardial infarction

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LONG TERM ANTICOAGULANT THERAPY FOLLOWING MYOCARDIAL INFARCTION

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1960

Omaha, Nebraska

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INTRODUCTION

Anticoagulants are at present important in the treatment of the acute phase of myocardial infarction. Their value has been established in a large number of exact clinical investigations. The possibility of long term prophylactic and therapeutic use was a natural sequence to its successful use for acute thromboembolic conditions. But in spite of the fact that coronary atherosclerosis causes so many deaths, efforts to prevent recurrent myocardial infarction by the long term use of anticoagulants have become popular only recently, because of the difficulties in obtaining accurate statistical analysis of the effect of long term therapy, because of the risk of inducing hemorrhagic complications, "and possibly because of the disinclination on the part of the physician to enter into a preventive regimen lacking the distinction of acute medical care." (1) Once it was established that prolonged anticoagulant therapy can be given on an ambulatory basis without any appreciable injurious effect (provided accurate supervision is possible) this therapy was increasingly used in a variety of cases including myocardial infarction. Initially, the published reports concerned very small groups of cases, but in recent years a number of larger series

with prolonged follow-up periods have been described. "A study of these publications shows that, although the results are generally described as favorable, it is exceedingly difficult to use the figures given as a basis for a definite conclusion regarding this therapy and regarding selection of suitable patients and determination of the duration of treatment. This difficulty is closely correlated with the fact that few definite data are available on the long term prognosis of untreated myocardial infarction." (2)

A great many factors are important in this prognosis: the patient's age, additional complications as hypertension and the extent and clinical severity of the infarction, as well as the many variables introduced by the active lives of the individuals.

Public interest in anticoagulant drugs has increased markedly and is reflected by the news concerning the President's use of an anticoagulant and more recently by the direction of the Senate Appropriations Committee to the National Institutes of Health to study the action and utilization of anticoagulant drugs as aids in the treatment of coronary and cardiovascular disease. The directive was backed by a two million dollar appropriation (Senate Report No. 17191, 88th Congress, 2nd session, page 28). Clinician and layman alike will

watch with interest a forecast recently made. "If these trends are corroborated (reduction of morbidity in coronary artery disease) long term anticoagulant therapy is the first distinct preventive agent in arteriosclerotic disease." (3)

The purpose of this thesis is to summarize a review of the literature on the principles and results of long term anticoagulant therapy, and to partially fulfill the requirements for the degree of Doctor of Medicine at the University of Nebraska College of Medicine.

HISTORY

Surprisingly enough, neurologists began first in using anticoagulants in long term therapy. They started a trial of continuous treatment with dicumarol of cases of disseminated sclerosis as early as May of 1942. (4) As far as can be seen from the literature it was Nichol (5) who introduced long term therapy into cardiology. He began the treatment in February 1944 of a patient who had three serious myocardial infarcts in thirteen months. At about the same time, Peters, Geyther, and Brambel (6) started using long term treatment in a few cases of coronary thrombosis in the hope of preventing recurrences. In the autumn of 1946 Wright and Foley (7) started continuous treatment with dicumarol in patients with rheumatic heart disease, atrial fibrillation and a tendency to recurring embolism. Allen, Hines, Kvale, and Barker (8) in 1947 and 1949 stated that the final occlusion in obliterating arteriosclerosis is nearly always due to thrombosis. They therefore have given some such cases protracted treatment with dicumarol for up to ten months.

In Norway, long term anticoagulant therapy was introduced by Owren (9) in 1948 and in 1952 he reported on his experiences with a group of 79 patients. He has

published several papers since that time on his results.

Sprague and Jacobsen (11) in 1948 initiated long term therapy in a patient with atrial fibrillation and recurring embolism. Olwin (12) in 1949 investigated long term therapy in 17 patients with different thromboembolic diseases for periods varying from four to twenty-three months.

Askey and Cherry (13) in 1950 treated 20 patients for an average of eleven months. Cosgriff (14) began long term therapy in 1950 and in his last paper in 1953 mentions 28 patients treated with dicumarol for an average of 223 months. Since then, many papers on long term treatment with anticoagulants have appeared gradually. Many of these publications are from medical centers in which the leaders and their different co-workers have published their experience at intervals dealing with an increasing number of patients who, as time passed, have had increasingly long periods of treatment. Further, there are a number of scattered publications dealing with different aspects of long term treatment. In practically all investigations long term anticoagulation therapy has given favorable results, and as a result of these favorable results long term treatment has been gradually accepted by clinicians and is now the recommended treatment in most cases of myocardial infarction.

PRINCIPLES OF LONG TERM ANTICOAGULANT THERAPY IN THE PREVENTION OF MYOCARDIAL INFARCTION

The basic effect of long term anticoagulant therapy is prophylactic in preventing thrombosis. When coronary thrombosis has already occurred, anticoagulation therapy is too late to influence irreversible myocardial damage. Owren (10) states that a more logical approach therefore seems to be the prophylactic treatment by continuous use of anticoagulant in all patients with coronary disease, since thrombotic occlusion or infarction may occur at any time. This approach leads to the use of anticoagulant for years and decades, in order to prevent coronary artery thrombosis. Prophylactic anticoagulant treatment along these lines raises two important questions:

1. Does reduced coagulability produced by oral anticoagulants prevent the formation also of intra-arterial thrombi? If such preventive effect exists, the next question will be

2. How frequent is thrombosis the cause of coronary occlusion?

As to the first question, it is unknown to what extent reduced coagulability actually inhibits the formation of thrombi. The mechanism of thrombosis involves several processes besides the clotting mechanism. Owren

states that platelet aggregation and adhesion of platelets to the endothelial wall, for example, are of major importance, and the interrelationship between platelet adhesion and the coagulation process is not clear, nor is it clear how anticoagulant affects this special function of the platelets in the thrombosis formation. (10) Some investigators have found that dicumarol, like heparin, exerts a retarding influence on development of experimental intravascular thrombosis in animals. One should be careful however in translating results of experimental studies in animals to clinical practice. Neither is it justified to interpret the results of anticoagulant therapy in acute myocardial infarction to mean that hypocoagulability also will provide effective prophylaxis against coronary thrombosis.

The second question: How frequent is coronary thrombosis as the cause of coronary occlusion? Clinical coronary occlusion is caused by narrowing or occluding of the coronary arteries by the atherosclerotic process per se, by thrombosis, or by subintimal hemorrhage.

On looking for the answer to the second question in the literature one finds the information is very variable, in fact in different investigations the incidence of thrombosis as the cause of coronary occlusion varies from 9 to 95%. This is probably due to the difficulty,

the different techniques, and the varying degrees of thoroughness in the post-mortem investigation into the occurrence of thrombosis in the coronary arteries. It is probably also partly because of variations in the type of case and in the composition of the different materials. But the majority of all investigators have concluded that thrombotic occlusion is an important pathogenic factor in about two-thirds of all cases of fatal acute myocardial infarction. Various factors in the pathogenesis of atherosclerosis such as dietary fat intake, stress, tobacco, and physical activity may well exert their influence also through an increased tendency for thrombus formation. It will be an important problem for future coagulation research to analyze the influence of these various factors in blood coagulability and tendency to thrombosis.

These scattered remarks show that knowledge about the mechanism of thrombus formation and the frequency of thrombotic processes in atherosclerotic disease is as yet insufficient. Therefore, the effect of long term anticoagulation therapy in the prevention of coronary thrombosis must be evaluated on the basis of clinical experience.

Indications for long term anticoagulant therapy. (16)

1) Continuing anginal pain after recovery from myocardial infarction.
2) Recurrent myocardial infarction, especially if thromboembolic complications are evident.
3) Development of coronary insufficiency suggesting an impending coronary occlusion, following asymptomatic post-infarction period.
4) Cardiac arrhythmias with embolism.
5) Chronic congestive heart failure.
6) In all patients with coronary disease who may or may not have had one or more episodes of myocardial infarction and who are intelligent enough to report periodically for prothrombin checks and to take the suggested dosage. (9)

Contraindications to long term anticoagulant therapy.

1) Absolute - situations in which anticoagulant therapy is inadvisable regardless of the strength of the indication for its use. (18)
   a) Purpura or hemorrhagic diseases of any type.
   b) Ulcerative lesions.
   c) Blood dyscrasias with a bleeding tendency.
   d) Subacute bacterial endocarditis.

e) Recent operation on the brain or spinal cord.

f) Inadequate facilities for determining prothrombin time.

g) Irresponsible or mentally deficient person. Alcoholic patient may be in this category. (19)

h) Physicians with little training or experience with anticoagulants, and those with inadequate laboratory facilities.

i) Marked hypertension above 200/110. (17)

2) Relative contraindications - situations in which the use of anticoagulant drugs may be attended by increased but not necessarily prohibitive risk. (18)

a) Hepatic insufficiency.

b) Renal insufficiency. (Meyer (20) places these two contraindications in the absolute category.)

c) Indwelling gastrointestinal tube such as a Miller-Abbott tube.

d) Dietary deficiency states.

e) Fever (?)

f) Active pulmonary tuberculosis. (17)

When relative contraindications are present one must balance the risk of therapy against the risk of thromboembolism if treatment is not administered. Unfortunately selection of patients for prolonged anticoagulant therapy is inexact, and at times hemorrhage may occur even when only a mild contraindication exists. In summary, a physician must rely on his clinical experience and these general principles to guide him in the selection of patients for long term anticoagulation therapy.

Instructions for patients or precautions.

1) The patients must be given the fullest information about all aspects of their treatment, such as the dose, strength of tablet, possible side effects, especially bleeding both externally and internally, (21) in which case the patient should report to his physican immediately.
2) All instructions should be written.
3) Other written precautions that should be given to the patient include:
    a) Need for regular attendance for prothrombin time test.
    b) Danger of taking certain drugs such as aspirin (not more than 1 gram per day)

Phenylbutazene, and broad spectrum antibiotic.

c) Before patient starts treatment he should be warned of the danger inherent in the treatment and of stopping too abruptly. (22)

d) A marked alteration in the amount of alcohol consumed daily may cause a fluctuation in the prothrombin time.

e) Instructions to inform any physician treating the patient that he is on long term anticoagulant therapy.

4) The patient should be given a card stating that he is taking anticoagulant and what the prothrombin time is, and in the event of hemorrhage call a physician or consult patient's doctor -- name and address, as he may require an injection of Vitamin K_1.

5) Each patient should be provided with two 10 mgm gelatin capsules of Vitamin K_1 to take by mouth if he notices bleeding from any of the body orifices and warned to contact his physician immediately if this occurs.

6) Any deficiency of Vitamin C should be cor-rected and an adequate intake in the diet insured.

7) If possible hospital treatment including blood transfusions should be within reasonable distance or on a vacation the dosage should be reduced 5 to 10% below that which ordinarily keeps the patient at an optimum level. (22)

8) The possible need to reduce, but not stop, the maintenance dose of the anticoagulant drug and the necessity to take more frequent blood tests during intercurrent illness are particularly stressed.

It goes without saying that complete patient cooperation is essential to properly controlled anticoagulant therapy.

Choice of drug.

There are commercially available at the present time eight prothrombin depressant drugs. Of these, six are coumarin derivatives:

1) Bishydroxycoumarin (Dicumarol)
2) Cyclocumarol (Cumopyran)
3) Ethyl biscoumacetate (Tromexan)
4) Warfarin (Coumadin)
5) Marcumar
6) Acenocoumarin (Sintron)

The other two are indandiones:

1) Phenindione (Hedulin or Danitone)
2) Diphenadione (Dipaxin)

The *in vivo* actions of the two groups of drugs appear to be grossly similar in nature in that they depress prothrombin and Factor VII, Factor IX, and to some extent Factor V. However there do seem to be differences between the various drugs in 1) the rate at which they reduce the plasma concentration of individual clotting factors; 2) the actual levels to which the factors are reduced; and 3) the rate at which the factors return to normal following withdrawal of the drug.

From the point of view of their overall induction and recovery periods the eight drugs may be grouped into three categories:

1) Bishydroxycoumarin and cyclocumarol having slow induction and slow recovery periods - 48 to 72 hours to take effect and lasting 48 to 96 hours or longer after being discontinued.
2) Ethyl biscoumacetate, Phenindione, and Acenocoumarin having rapid induction and rapid recovery periods - 18 to 24 hours to act and activity only lasting 12 to 30 hours after being discontinued.
3) Diphenadione, Marcumar and Warfarin providing rapid induction and slow recovery. Induction period is from 24 to 36 hours and recovery takes from 10 to 20 days after the drug has been discontinued.

There are no particular advantages to Bishydroxycoumarin and Cyclocumarol except those of known reliability and familiarity. They are safe and efficient and as satisfactory as any of the others for long term therapy. The drugs with shorter induction and recovery periods provide for earlier control and also provide for more rapid decontrol in case of hemorrhage, trauma or required surgery. The patient and physician using them must be aware of the importance of regular dosage, since the omission of one day's dose may result in "escape" from the therapeutic bracket. In the case of Phenindione, it is wise to use the divided daily dose in order to prevent such escape. (23)

Those drugs with short induction periods and prolonged recovery times, Diphenadione, Marcumar, and Warfarin, have the advantage of a lesser tendency to produce variations from the therapeutic bracket (20 to 40% of normal prothrombin), and the omission of one or two doses can readily be compensated for before the prothrombin "escapes" from this bracket. This property of a long recovery period is a disadvantage in case rapid return to higher prothrombin levels is desired in the event of serious bleeding or the necessity of early surgery. This disadvantage, however, may be completely overcome by the administration of Vitamin K active substances.

If short term therapy is anticipated, one of the drugs from group 2 may be selected to advantage. They also may be chosen in cases which may require surgery within a short time after therapy is instituted.

For long term therapy, on the other hand, the clinician will find long acting anticoagulants of group 3 quite satisfactory. A large number of investigations reporting in the literature prefer Warfarin sodium. Brotman (7) adequately summarized the advantages of Warfarin. He states that "of all the anticoagulants, Warfarin seems to be the closest approach to the ideal." It is capable of rapidly producing a high hypoprothrominemia which is well sustained, stable and readily counteracted by soluble menadione and Vitamin K as well as Vitamin K_1. Minimal toxicity accompanies Warfarin at therapeutic levels, and bleeding occurs with relative infrequency even though severe hypoprothrombinemia results from overdosage. The important advantage of Warfarin is that it can be administered orally, subcutaneously and intravenously in low dosages. (11) It is available in tablets of 5, 10, and 25 mgm. and 10 cc. ampules containing 75 mgm.

The indondiones have a number of drawbacks.

1) Patient resistance is high and valuable time may be lost before this is discovered.

2) They have been known to produce toxicity. There has been mention of several cases of agranulocytosis (24, 25) and dermatitis (24) reactions reported in the literature. Ager (25) states agranulocytosis should be looked for 20 to 30 days after treatment has begun. Meyer (20) admits that such toxic reactions with indandiones are rare but as he sees it, none of these reactions result from any coumadin compound, and since there is no significant advantage in indandiones, he avoids the small hazard of serious complications.

3) Phenindione imparts an orange color to the urine and where the patient has been instructed to watch for any change in the color of the urine that might indicate bleeding, this could be confusing.

Dosage

Anticoagulant Dosage (27)

Coumarin Derivatives	Average doses (controlled by prothrombin time)		
	1st dose	2nd dose	Maintenance
Dicumarol	300 mg.	100-200 mg.	25-100 mg.
Tromexan	1500	900	300-900
Cumopyran	150	75	50-75
Marcumar	21	9	3
Warfarin sodium	50-75	25-40	5-10 daily
Acenocaumarin	16-28	8-16	2- 8
Phenindione	150	50-75	25-75
Dephenadione	18	9	3- 6

The selection of which anticoagulants to use must be based on what the clinician wishes to accomplish in terms of rate of action and his familiarity with the tool he is to use. There is no evidence that the therapeutic effectiveness is dependent on the specific drug used, but only on the prothrombin levels maintained.

Technique used:

The patient is preferably admitted to the hospital where an endeavor is made to standardize dosage requirements. (19) The dosage must be individualized by daily prothrombin time determination. Roughly the dosage as given in the preceding table can be followed. When the prothrombin time goes below 20%, the dose should not be given that day (except the drugs that have rapid recovery rates and then only a part of the dose is given.) When the prothrombin time goes above 40% the dosage is increased accordingly. In most cases the dosage can be stabilized after 7 to 10 days or less. (19) But no two patients respond exactly alike and occasionally there are patients who are unduly responsive or resistant to coumarin anticoagulants; therefore the dosage must be modified accordingly.

After the stabilizing dose has been determined, the patient is maintained on this dosage with prothrombin time tests taken once a week or oftener. The time

interval should be determined by the clinician's assessment of that particular individual's overall circumstances. In the literature the time interval for prothrombin time determination is quite controversial and varies from two times a week to once every four weeks. But due to the individualization of this form of treatment, the statement made above should suffice.

The dosage requirements will vary from time to time but over a period of years the average of a specific patient will remain fairly constant in most instances.(19) The greater the care taken to determine the exact maintenance dose, the smaller the fluctuations in prothrombin times, and also the less frequent the need for blood tests. (21) Toohey also states that in his experience with long term anticoagulant therapy it is amazing how stable the requirements of the majority of patients with regard to the dose of anticoagulant drug, provided that there is not intercurrent illness or marked change in diet and that the patient is not taking certain drugs which may interfere with the treatment. The desired levels of prothrombin time and the frequency of prothrombin time tests will be discussed further under "Control."

Side Effects:

Bleeding and its consequences are the main dangers that need concern the clinician and the patient. (26)

This will be discussed further under "Hemorrhage." Dermatitis has been observed during the administration of Tromexan and Phenindione (24), and may be of some inconvenience and discomfort to the patient. However, it disappears when the drug is discontinued.

Several cases of agranulocytosis have been reported with the use of Phenindione, which has been discussed.

Of minor importance is occasional nausea following a loading dose of prothrombin depressant, particularly Dicumerol. For this reason it is helpful to give a loading dose, no matter what the drug, in divided doses 30 to 60 minutes apart.

Countermeasures:

It may be necessary at times to neutralize rapidly the effects of anticoagulant drugs. This may be as a result of hemorrhage, trauma, or required surgery. The introduction of Vitamin K_1 which is very active when taken orally, has greatly added to the safety of the use of the prothrombin depressant drugs. Ten to 50 mg. of Vitamin K_1 in orange juice or on a piece of food will reduce the prothrombin time within 3 to 6 hours and the duration of this action can be fairly well controlled according to the size of the dose. (27) In the event of serious hemorrhage, Vitamin K can be given intravenously and may be repeated every 4 to 6 hours until the plasma

prothrombin activity is normal as shown by serial determinations of plasma prothrombin time. Restoration of normal blood volume may be required if severe loss of blood occurs, and stored blood is satisfactory for this purpose; it is not necessary to administer fresh blood.(18)

If the hemorrhage is not severe, i.e., is limited to hematuria, gross or microscopic, and/or mild bruising, and if the prothrombin time is above 5% by the one stage method, withdrawal of the drug may be all that is necessary. This is particularly true if the drug is one characterized by a short recovery period.

It is not necessary to use Vitamin K when the patient's prothrombin time is below 10% of normal and no bleeding is present, even with the longer acting drugs. Withdrawal of the drug and careful observation of the prothrombin level is the more desirable procedure. (23)

When given in large amounts the water-soluble, Vitamin K active substances are effective against all prothrombin depressants except Dipaxin and Miradon and these substances do not render the patient refractive to further anticoagulant administration. It is usually possible to titrate the prothrombin back to the therapeutic bracket with small amounts of Vitamin K_1, and thus refractility to further anticoagulant administration can be prevented. When one is trying to counteract the effect

of Dipaxin small amounts (5 to 20 mg.) of Vitamin K_1 can be used. Olwin (23) states that his group prefers to use the water-soluble Vitamin K active substances rather than the fat-soluble substances such as Vitamin K_1 or the oxide because the latter often render patients refractile to further prothrombin depressant administration for a period of days to weeks and if further therapy is contemplated, they should be used with caution. The water-soluble Vitamin K products available are:

1) Menadione sodium bisulfate. (Hykinone) Available in tablets of 5 mg. and 1 cc. ampules containing 2.5, 5 and 10 mg. and 10cc. ampules of 72 mg.

2) Sodium Menadiol diphosphate. (Synkavite) Available in tablets of 5 mg. and 1 cc. ampules containing 5 and 10 mg. and 2 cc. ampules of 75 mg.

Olwin (26) gives the water-soluble vitamins in doses of 100 to 200 mg. intravenously over protracted periods of 3 hours. The fat soluble vitamins or Vitamin K_1 is phytonadione or K-phytonadione oxide (Mephyton). It can be given intravenously, intramuscularly or orally. It is available in tablets containing 5 mg. and as Mephyton emulsion for slow intravenous injection, in 1 cc. ampules of 50 mg. The initial dose is 50 to 100 mg. which may be repeated as often as necessary until the desired effect is produced. (17) Shapiro and Spitzer suggest

that ascorbic acid and Vitamin "P" factors should be used in all cases receiving anticoagulants. When it was used prophylactically, there was not a single case of bleeding. (17) There is no evidence at the present time that excessive amounts of Vitamin K contribute to thrombosis.

Withdrawal of Anticoagulant Therapy.

Withdrawal or decontrol of anticoagulant drugs ordinarily presents no problem. Since thrombosis has occurred in some instances when the drugs have suddenly been withdrawn, it is usually safer to discontinue them gradually. This provides for a slow return to normal prothrombin levels, and the latter may be checked at monthly intervals for a two-month period.

The technique of decontrol is quite important if the patient has atrial fibrillation and a history of embolism. In general, these patients should receive continuous anticoagulant therapy until after conversion to a normal rhythm.

When patients on anticoagulant therapy require surgery, the prothrombin depressant should be withdrawn and intravenous heparin given as soon as the prothrombin rises above the therapeutic bracket. This must be repeated at four hour intervals while decontrol is in progress. Once daily, the interval is extended to 6 hours

and a prothrombin assay made at the end of that time. This is necessary because heparin interferes with the prothrombin assay and the heparin effect must be eliminated before the blood samples for the prothrombin determination are drawn.

Surgery can be carried out when the prothrombin has reached 75% or more, but the heparin is continued until 4 hours prior to surgery. It, along with the prothrombin depressant, is started again 6 hours following surgery and is continued until the prothrombin is again within the therapeutic limits. Olwin (26) states that he has seen fatal emboli when such a routine has not been followed.

Methods of Control.

The sine qua non of long term anticoagulant therapy is a reliable laboratory. (28) The busy clinician will have much less worry if he knows the laboratory is giving him accurate prothrombin time determinations. The safe and effective administration of the prothrombin depressants is dependent upon a reliable method of control. This, unfortunately, is not generally available at the present time. Until recently the so-called prothrombin depressant drugs were considered to affect primarily prothrombin and to have little influence on the clotting factors. There is growing body of evidence,

however, to indicate that factors other than prothrombin, particularly the accelerators, Factor VII, and to a smaller degree Factor V, are also reduced. Furthermore, plasma thromboplastin component (Factor IX, Christmas factor), a plasma constituent essential to the formation of thromboplastin in blood, has been reported by a number of workers to be depressed by a variety of anticoagulants. (29) It appears that the reduction of various coagulation factors as a result of therapy varies from drug to drug and patient to patient, and it is quite possible that additional known or still unknown factors may be affected.

The administration of anticoagulants is controlled almost universally by means of the one stage prothrombin assay (Quick's Method). This involves the addition of tissue juice (thromboplastin) to oxalated or citrated plasma, subsequent recalcification, and measuring the time of the appearance of fibrin. Some laboratories report their results in seconds, others preferring to convert the observed time to "percentage prothrombin." The advantages of the latter are as follows:

1) It places the burden of accuracy on the laboratory.
2) It provides for less variation in interpretation.
3) It provides for easier control when the patient moves from one geographic area to another and

blood samples are processed by different laboratories. When the results are expressed in terms of percentage prothrombin it is advisable to run a "normal curve" once a week and more often if the batch or type of thromboplastin is changed.

One of the variables of the one stage test is the recent discovery that the various thromboplastin preparations used in the assay, all of which are animal or human tissue in origin, contain varying amounts of Factors V and VII. Thus, we may be adding to the test some of the very factors which we are assaying. These differences in the thromboplastins themselves are, at least in part, responsible for the varying prothrombin results obtained from time to time, and hence the resulting occurrance of unexpected hemorrhages in some cases and the apparent failure of anticoagulant therapy in others. Despite these difficulties many patients are being given anticoagulants with apparent safety and benefit. Thus, when administered carefully, the advantages of therapy far outweigh its possible disadvantages.

More recently Owren's "P and P" (prothrombin and proconvertin) technique has been advocated as being more sensitive and reliable, and it is claimed that with its use there is a lower incidence of hemorrhagic manifestations. (30) While this procedure is also influenced by

the addition of Factors V and VII in the thromboplastin, the two stages of the clotting mechanism are separated, and practiced experience has shown that they produce considerably less variable prothrombin results than the one stage method.

A comparison was made between Quick's and Owren's methods at the anticoagulant unit, New End Hospital in London where 2,000 blood samples were tested with both techniques over a period of 16 months for the control of in-patients on anticoagulant treatment. (30) As a result of this trial there appeared to be no doubt that Owren's method had one decided advantage in that it reflected changes in the prothrombin level (meaning both prothrombin and proconvertin), or even more hours earlier than did Quick's method. (24) The great advantage of Owren's method was therefore that one was able to make the necessary adjustments in dosage more quickly and easily. This meant that the correct maintenance dose of the anticoagulant was more quickly arrived at and lessened the number of blood tests required for control of the treatment. It has been said that because Owren's method is more sensitive than Quick's, it enables a more accurate estimate to be made of the dose of the anticoagulant drug required. But this is not strictly true. Quick's test is just as sensitive to the effects of small changes in the dosage

of anticoagulant drugs but it takes longer for these effects to be noticeable. Therefore, with long term anticoagulant therapy, when blood tests are made every few weeks, or even longer, it is difficult to see how Owren's technique will materially improve on Quick's method. Especially in a busy out-patient clinic, where large numbers of tests have to be made quickly to avoid keeping the patients waiting too long, the speed and simplicity of Quick's method are a decided advantage.

The desirable level of prothrombin time for patients on long term therapy is somewhat variable among the various investigators in the literature. The range is from 23 to 40 seconds or two to three times the normal control. Most of the investigators followed the rule that two or two and one-half times the normal prothrombin time expressed in seconds was an adequate level for the ambulatory patient on long term anticoagulant therapy.

Nichol (1) and his group kept the prothrombin time at two and one-half times the control with 1,091 patients over a ten-year period. This allowed a range of 24 to 38 seconds, as the average normal obtained was 13.5 ±1.5 seconds. When compared to serial dilution curves, the range of 24 to 38 seconds is equivalent to 30 to 10% of prothrombin activity.

A large number of investigators reporting in the literature using percentage of prothrombin activity recommend a range of 40% to 20% of prothrombin activity.

Wright (19) recommends a range of 50 to 25% prothrombin activity in the ambulatory patient because he is subject to more trauma and dietary disturbances that may affect anticoagulant utilization than is the patient under complete hospital control.

Again the clinician should use his clinical judgement in assessing each patient's circumstances, intelligence and idiosyncrasies as to what prothrombin level he should be safely maintained.

Factors Influencing Uniformity of Control.

It is well for the clinician to be aware of factors other than those in the laboratory which may be responsible for variations in the control of anticoagulant therapy. Among these are the general nutritional state of the patient, his diet, other drugs he may be taking, his habits with respect to alcohol, his ability and will to cooperate, individual tolerances and idiosyncrasies which are not at this time too well understood, and of course the experience of the clinician with any particular drug. A patient with generally good nutrition will be easier to control than one in a poorly nourished state. A diet poor in proteins appears to be associated with

frequent variation in prothrombin levels.

The methylxanthines and some of the tranquilizing drugs may increase the tolerance to prothrombin depressants. A sudden rise in prothrom bin time which does not respond to an increased dose of anticoagulant in a few days should lead the clinician to suspect that one of these drugs may have been introduced into the patient's routine. On the other hand, salicylates, which break down to coumarin substances, may precipitate a drop in prothrombin levels. Patients should be cautioned against taking more than one gram of salicylate a day. Alcohol elevates prothrombin levels, and patients who use alcoholic beverages must be advised to take the same amount daily or quit altogether in order that their anticoagulant intake may be adjusted to it.

The irresponsible patient will, of course, make for more difficult control, for he may be irregular in taking his medication and in following instructions otherwise. Olwin (26) and Koppel make up a chart for the patient and insist that he checks off the dosage each time the drug is taken. They find that this is especially valuable in elderly patients. It is often well to delegate the responsibility for administration to a competent member of the family.

The physician should become acquainted with at least two types of prothrombin depressants, for when he encounters a patient in whom control is difficult, he may wish to shift to another of the drugs.

Frequency of Prothrombin Time Determinations.

In the literature the recommended frequency varies greatly. The range is from one to twelve weeks.

1) Olwin (26) and Koppel recommend no longer than two weeks between tests.

2) Toohey (21) controlled 105 out of 117 patients by testing every 6 to 12 weeks. The unstable ones were tested every 2 to 4 weeks.

3) Jolly (31) recommends intervals of 7 to 14 days.

4) Loughridge (22) recommends no longer than 8 days.

5) Nichol (1) and his group gradually increased the length of time between tests in their series of 1,091 patients. They started at 10 days, increased to 12 days, and then to 14 days. After 6 months of treatment in patients who seemed exceptionally stable, the interval between tests was extended to 21 days.

The length of the interval between prothrombin tests should depend upon the stage of therapy, the stability of the individual patient's prothrombin level, the dependability of the patient, and, to some extent, on the particular drug in use.

Hemorrhagic Complications.

When a patient is on ambulatory anticoagulants a certain risk of hemorrhage is to be assumed. (32) Easy bruising, slight amounts of blood on the toothbrush in the morning, or on the handkerchief when blowing the nose a little too vigorously during an upper respiratory infection, is found in almost every patient who is carried on anticoagulants for any length of time. Therefore, a fairly large number of minor hemorrhagic tendencies is seen in patients on longterm anticoagulant therapy.

The most frequent minor hemorrhage seen is small ecchymosis of the skin, microscopic blood in the urine, and epistaxis. Tanzi (32) found, in treating 213 patients on long term anticoagulant drugs, that hematuria was the most frequent (24 cases) single complication. Hematoma, hemoptysis, bleeding from gums, bleeding from hemorrhoids, melena, vaginal bleeding, hemarthrosis, retinal bleeding, or excessive menstrual bleeding are other types of bleeding which are frequently encountered in patients on long term anticoagulant therapy.

Tulloch (33) has found that the majority of bleeding episodes occur when the prothrombin time was over 25 seconds, or between 25 and 39 seconds. But bleeding is much more common when the prothrombin time is over 40 seconds.

Treatment of bleeding in most cases consisted of the adjustment or temporary cessation of the anticoagulant until the bleeding had ceased. Anticoagulants need not be stopped when the bleeding is slight and the prothrombin time low, for example as in subcutaneous ecchymoses, or slight bleeding from the gums or hemorrhoids.

If the bleeding continues, the patient should be given one of the Vitamin K preparations to hasten the return of the prothrombin content of the blood to normal levels. If the hemorrhage is severe, the patient should be transfused as rapidly as possible with whole, fresh blood.

Tulloch (33) found a number of cases in which the prothrombin time was quite high but the patients experienced no bleeding. He usually stopped the dose of the anticoagulant until the prothrombin time had returned to a safe level and then re-instituted the therapy.

Occasionally massive hemorrhage is encountered, especially from the gastrointestinal tract, genitourinary system, hematemesis, cerebral hemorrhage or other sites of bleeding. In these cases the patient should be transfused and given Vitamin K_1 intravenously with discontinuance of the drug.

Other hemorrhagic complications of long term anticoagulant therapy are reported in the literature, thus:

1) Goodman (34) reported a fatal case of acute nonspecific pericarditis with cardiac tamponade.

2) Chokas (35) reported a fatal case of bilateral adrenal hemorrhage complicating dicumarol therapy for myocardial infarction.

3) Cloward (36) reported on a case of spontaneous intraspinal hemorrhage and paraplegia complicating dicumarol therapy.

4) Waldron (37) in 1954 and several others since have reported cases of myocardial rupture and hemopericardium associated with anticoagulant therapy. They showed that myocardial rupture occurred in 14.1% of anticoagulant patients treated and 4.98% of untreated cases. They also showed that hemopericardium was more prevalent with increased anticoagulant effect.

5) Ziffer (38) and others have reported profound bleeding after dental extractions during dicumarol therapy.

6) Many cases of bleeding from the gastrointestinal tract either as hematemesis or melena due to neoplasm or ulcerative lesions have been reported.

7) Cerebral hemorrhage has occurred in a number of cases. This can be a serious complication in the presence of bacterial endocarditis and anticoagulants should be used with caution.

Hemorrhage has been the main argument against the use of anticoagulants. It is rarely of serious degree but fatalities do occur. (17) With the advent of Vitamin K_1 preparations, the possibility of severe hemorrhage is becoming less and less an objection to this therapy.

Nichol (1) and his group in their series of 1,091 cases over a ten-year period and 6 fatal cases due to hemorrhage, or 0.5%, reported 4 cases of cerebral hemorrhage and 2 with subendocardial hemorrhage.

Ensor (39) and Peters report that in 268 patients on long term therapy not one fatal hemorrhage occurred.

Thromboembolic Complications of Long Term Anticoagulant Therapy.

This complication includes all cases of vascular occlusion and its sequelae whether fatal or non-fatal. A more extensive discussion of the fatal cases will be covered under "Results."

Most of the non-fatal cases of thromboembolic complications are reported as recurrent myocardial infarction, pulmonary emboli, peripheral emboli and phlebothrombosis. Although there are cases of visceral and cerebral embolus reported in different series, they are not fatal.

In reviewing the literature of non-fatal thromboembolic episodes in approximately half of the cases reported the prothrombin time was in proper control, and in others it was below the accepted therapeutic range and

the patient was more susceptible to thromboembolism. Therefore, at no level of prolongation of the prothrombin time was complete protection provided from thromboembolic episodes.

There is no study which gives results on the number of fatal cases of thromboembolism compared to the non-fatal cases. In most all of the studies the conclusions were based on death rates alone.

Duration of Treatment.

The length of time a patient should be kept on long term anticoagulant therapy varies greatly with different writers. A few recommend that the patient be continued on this therapy for the balance of his life, though others recommend varying lengths of time.

1) Estes (18) suggests 6 to 12 months after the last thromboembolic episode.

2) Breddin suggests one and one-half to 2 years.

3) Borg (40) suggests 2 years at least and perhaps indefinitely.

4) Ashey and Cherry (13) suggest 2 years.

5) Foley (7), Wright and Suzman and others suggest stopping after 3 years of freedom from symptoms.

6) Tulloch (33) and Wright have a few patients who have been under treatment for 8 years.

7) Putman (28) has some patients on treatment for 9 years.

8) Loughridge (22) has had some younger patients (forties and early fifties) on anticoagulant therapy for 4 to 5 years without a mortality.

Here again the physician's clinical judgement should be the deciding factor. That particular individual's treatment plan should be based on the patient's age, occupation, intelligence, and all other circumstances important to the evaluation of that individual's care.

RESULTS OF LONG TERM ANTICOAGULANT THERAPY REPORTED IN THE LITERATURE

In spite of the importance of coronary atherosclerosis, survival rates after a first attack of acute myocardial infarction are not yet clearly established, but long term follow-up studies are appearing. A striking feature is that the various investigators use different methods to express their findings, thus precluding any comparison of results obtained by different investigators. Several authors merely present the therapeutic results obtained in a group of selected patients without controls. Obviously such data warrant only preliminary conclusions, particularly since the period of observation is brief, and since detailed clinical findings are lacking.

Nevertheless, a review of the results of the majority of investigators in this field will be presented.

1) In 1954 Nichol (42) and co-workers reported on 295 patients with coronary disease on long term anticoagulant therapy. The duration of treatment ranged from 3 months to 7 years. To summarize the results in these 295 patients, there were 41 deaths (13.8%) and 7 recurrences, while in the control group of 110 patients (after anticoagulant was stopped) there were 37 deaths (33%) and 14 recurrences.

In 1955 Foley (43) and co-workers reported on 300 out-patients with myocardial infarction treated with long term anticoagulant therapy. They summarized 23 cases as follows: In 11 patients who had had two or more episodes before therapy and who were not given anticoagulant therapy over a period of 587 months, there were 49 thromboembolic episodes, including 30 instances of myocardial infarction and 10 of pulmonary embolism. When anticoagulants were given over a period of 393 months there were 3 thromboembolic episodes; when anticoagulants were given over a period of 554 months there was only one episode.

3) Stephens (41) in 1954 pointed out that long term anticoagulant therapy can be carried out in private practice. He reported on 53 cases with an average treatment period of 10 months; of the group, 10 died of causes not associated with therapy; 7 dropped anticoagulants against advice, and 5 of these died of myocardial infarction. Twenty-six were still on anticoagulants without untoward episodes of bleeding or thromboembolism.

4) Tulloch and Wright (33) reported on 227 patients who were treated with anticoagulant on an out-patient basis for 4 weeks or longer. Twenty patients had died, of whom 11 were still receiving anticoagulant at time of death; the others had stopped taking anticoagulant for various reasons. There were 40 incidents of thromboembolic complication without death.

5) Suzman (44) and associates reported on 82 cases in 1955 which had been treated for periods of 3 to 76 months after coronary thrombosis. Summarizing their results: In the long term group the mortality was 7.3% and there were 7 recurrences (8%); in the control group the mortality was 33% and there were 24 recurrences (27%). In patients with severe disease who were given long term anticoagulant therapy the mortality was 9% and there were 7 recurrences; in the control group with severe disease, the mortality was 46.7% and there were 21 recurrences. The mortality was 14.3% before therapy was started in patients with severe recurrent disease; it was 66% in the control patients with severe disease.

6) Muri in 1955 reported on 67 patients with coronary heart disease who have been on anticoagulant therapy for a total of 117 years with an average of 1 3/4 years per patient. Five patients died while under treatment, 2 from myocardial infarction and 3 suddenly at home. The drug had been discontinued in 6 patients.

7) In 1956, Keyes (45) and co-workers reported the following mortality in connection with long term anticoagulant therapy after myocardial infarction: After one year had elapsed, in control patients with a single episode the rate was 16.1% and in those with recurrent disease it was 31.2%, while in patients given anticoagulant

the rates were 4.2% and 8.0% respectively. After 2 years in control, patients with a single episode, the rate was 27.9% and in those with recurrent it was 39.6%, while in patients given anticoagulant the rates were 5.6% and 8.0%. After 3 years, in control patients with a single episode the rate was 31.7% and in those with recurrent disease it was 52.1%, while in patients given anticoagulant the rates were 8.4% and 10.0% after 4 years in control patients with a single episode the rate was 41.1% and in those with recurrent disease it was 62.5%, while in patients given anticoagulant the rates were 8.4% and 12.0%.

In their series, the single infarction group consisted of 186 controls and 71 treated patients. In the recurrent infarction group there were 48 controls and 50 treated patients. The period of treatment ranged from 6 months to 5 years. These workers found the death rate in the group with single infarction to be three times greater when anticoagulants were not given. They also found that in the recurrent infarction group the death rate was five times greater without anticoagulant therapy.

8) Manchester (46) in December, 1957 reported an interesting study on a group of patients given long term treatment with anticoagulant after myocardial infarction, and a control group given an ascorbic acid placebo; there were approximately 200 patients in each group. He found

the incidence of subsequent infarction to be three times greater in the control group than in the treated group; the mortality was eight times more in the control group than the treated group. Manchester found that the development of angina pectoris subsequent to myocardial infarction was the same in his treated as in his control group. In the anticoagulant group this occurred in 74 (36.2%). In the anticoagulant group, 38 (51.3%) showed improvement as indicated by increased tolerance in walking and performing the Master's two step test. In the control group, 20 (27.5%) showed improvement. In the anticoagulant series there were 4 deaths (5.4%); in the control series there were 30 (41.6%).

9) Owren (10) in 1957 reported a series of 229 patients treated over a period of 6,166 months. Seventeen patients discontinued the treatment. Twenty-nine patients under treatment died. So the mortality in 514 treatment years was about 5% per year.

10) Bjerkelund (47) reported in an excellent paper in 1957 which consisted of 237 cases, 119 in the treated group and 118 in the control group. In the treated group there were 22 cases (8.5%) of recurrence of myocardial infarction with 9 deaths. In the control group there were 38 cases (32%) with recurrence of infarction and 21 deaths of this number.

11) Tanzi (32) and Van Ness reported on 213 patients in 1957 under treatment for a total of 15,538 weeks or 72.9 weeks per patient. Thirteen patients (6.1%) died while on therapy and six of these from recurrent myocardial infarction.

12) Bengtsen (48) and Aspenstrom reported on 82 cases in 1957 who had been under long term anticoagulant therapy for 6 months or longer. Of these, the treatment was discontinued on 12 patients for various reasons. Eight patients died during treatment, three of which deaths were due to non-thromboembolic causes and five to recurrent myocardial infarction. In the remaining group of62 patients there have been no thromboembolic complications during an average time of treatment of 14.5 months.

13) Toohey (21) reported on 226 patients in 1958 who were treated with long term anticoagulant therapy following myocardial infarction. The total mortality rate for all these patients was 2.6%, 6.4%, and 13.2% in 6, 12, and 18 months.

14) Nichol (1) and his group in 1958 reported on the greatest number of cases of any study yet done in this field. They presented a pooled investigation of 1,091 patients with coronary atherosclerosis treated with long term anticoagulants for 3 to 100 months for a total of 24, 454 months with an average of 22.4 months.

Of these patients, 4.3% developed non-fatal thromboembolism, and 131 patients (12.0%) died on the regimen, mostly from cardiac disease. Three hundred-nineteen patients (29.2%) abandoned the regimen; an average of 18.4 months follow-up of these showed that 28.2% died within 4 years chiefly from cardiac disease and these 319 patients served as controls. Six hundred-sixty-nine (61.3%) continued the regimen an average of 27.6 months of therapy. As additonal controls, the investigators used 417 patients not given anticoagulants. Of these, 37.4% died, the majority from cardiovascular disease.

Patients without frank infarction:

Treated group - 96 patients, 6 deaths - 6.2% mortality; abandoned group - 32 patients stopped after 315 months - were followed for 732 months - 18.7% mortality; control group - 10 patients observed 269 months - 4 died or 40% mortality.

Patients after one infarction:

Treated group - 735 patients - 73 deaths - 10% mortality; abandoned group - 205 patients stopped treatment after 2,423 months - 18.5% mortality; control group - 297 patients observed 12,376 months - 110 died - 37% mortality.

Patients after multiple infarctions:

Treated group - 260 patients - 52 deaths - 20% mortality; abandoned group - 82 patients stopped treatment

after 1,246 months - 56.1% mortality; control group - 110 patients observed 3,276 months - 42 died - mortality 38.1%.

15) Tandowsky in 1959 reported on a group made up of 70 treated patients and a control group of 70. The anticoagulant phenindione was used exclusively in the treated group for an average of 3 years and 5 months per patient. Nine deaths occurred in the treated group (13) and only 2 of these were due to thromboembolic complications. In the control group 37 patients died (53%), 21 of whom were due to thromboembolic causes. Another interesting finding was that 46 of the treated group had relief of their cardiac symptoms as opposed to 22 of the control group. Forty-seven of the treated group were able to return to gainful occupation while only 21 of the control group were able to do so. There were only 3 cases of recurrent thrombosis or infarction in the treated group while there were 24 in the control group. This report was highly favorable to the long term anticoagulant treatment of myocardial infarction.

16) In 1959 in a Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council in London (49), a study was presented of 383 patients, 188 of whom received low doses of phenindione (1 mg. daily) and 195 received a therapeutic dose of the same drug. Of the 188 low-dosage group, 23 were

withdrawn from the trial. Of the high dosage group, 24 were withdrawn. There were 31 deaths among the low-dosage group, 28 of which were caused by recurrent myocardial infarction. There were 22 deaths in the high-dosage group, 18 of which were caused by myocardial infarction. It was also found that under the age of 55, males on high doses suffered recurrent infarctions at only 1/5 the rate of those on low dosage, and over that age the rate is halved by high dosage. These differences are statistically significant.

17) Ensor (39) and Peters reported a study in 1959 of 268 patients who received long term anticoagulant therapy after myocardial infarction. One hundred-forty patients discontinued the treatment and in the group the 5-year mortality rate was 29.3%; after 10 years it was 35.7%. Of the total of 52 deaths in the first 5 years, 42 occurred in the first 2 years that treatment was stopped. There were 62 deaths in the treated series or 23.1% of the total series. Of those who died while on anticoagulant therapy, the recorded prothrombin time was below 20 seconds in 28 cases. In the 10-year group the mortality in the treated series was 24.6% compared with 67.6% in the true control group.

As can be seen after reading the above lists of results, interpretation is made very difficult because each

investigator uses different methods to express his results. But from the reports the evidence is quite favorable for long term anticoagulant therapy following myocardial infarction.

SUMMARY

Coronary thrombosis in middle life is the most important cardiovascular disease. It is the principle cause of death after the age of 40. Following recovery from acute myocardial infarction, whether mild or severe, good or poor risk, subsequent recurrence is inevitable. It has been stated that there is a mortality of 25% in the first year, 50% in the second year, and 75% of patients do not live more than 5 years. Although extensive investigation in the pathogenesis of atherosclerosis continues, there is no specific treatment for coronary atherosclerosis. Likewise, though our knowledge of blood coagulation has increased, we still do not know why intravascular thrombosis occurs.

Reports on long term anticoagulant therapy indicate that the grave prognosis noted above following myocardial infarction can be prevented. The successful reduction of mortality and of thromboembolic complications in acute myocardial infarction by anticoagulants has justified the trial of continuous long term anticoagulation.

The history of long term anticoagulation was first written by, surprisingly, two neurologists in 1942. (4) Nichol (5) introduced long term anticoagulant therapy into cardiology in 1944. Since that time there has been a gradual acceptance of its value in long term therapy.

Long term follow-up studies on survival rates are gradually appearing in the literature. Most of the information being presented is quite favorable to the use of long term anticoagulants following myocardial infarction.

The basic effect of long term treatment is prophylactic in preventing thrombosis. This is achieved by depressing the patient's blood clotting mechanism so that thrombosis will not form. To accomplish this in the ambulatory patient so that his mode of living will not be completely upset due to fear of hemorrhage requires that many precautionary measures be taken. The selection of the patient is important. Long term therapy is indicated in all patients who may or may not have had one or more episodes of myocardial infarction, and who are of fair intelligence, cooperative, and able to follow instructions and report periodically for prothrombin checks. Of course any hemorrhagic tendency, ulcerative lesion, or any condition which may lead to bleeding when the patient is given anticoagulants is contraindicative. The patient must be given the fullest information about all aspects of his treatment, the drugs which should not be taken, and what course to follow in case of bleeding. Patient cooperation is essential to long term anticoagulant therapy.
The choice of drug in this therapy should be one which will depress the prothrombin time rapidly, whose

dosage is easily stabilized and will remain stable over long periods; one with a long recovery period after the drug is discontinued; one with lack of side effects, and one whose effects can be countered immediately in case of hemorrhage. Warfarin comes closest to meeting the above conditions of the eight anticoagulants commercially available. With Warfarin bleeding occurs relatively infrequently even though severe hypoprothrombinemia results from overdosage. It can be given orally, subcutaneously, or intravenously in low dosages.

To properly anticoagulate a patient, he should be hospitalized and the dosage regulated by daily prothrombin determinations. The dosages must be individualized as no two patients respond exactly the same. In most cases the dosage can be stabilized after 7 to 10 days, and the patient should be maintained on this dosage with prothrombin time tests taken at least once every 2 to 3 weeks depending upon that particular individual and his circumstances.

Bleeding and its consequences are the main dangers that need concern the physician and the patient.

It may be necessary at times to neutralize rapidly the effects of anticoagulant drugs as a result of hemorrhage, trauma or required surgery. Vitamin K and Vitamin K_1 products are commercially available which will reduce the prothrombin time in 4 to 6 hours. They can be given

intravenously or orally and are relatively safe.

The safe and effective administration of long term anticoagulants is dependent upon a reliable laboratory which produces accurate prothrombin time determinations. The one stage prothrombin assay (Quick's method) is used almost universally. It is a sensitive, accurate and reliable method of determining prothrombin time in continuous anticoagulant therapy.

There are factors other than the laboratory which may influence the uniformity of control, and must be watched for. Among these are the patient's nutritional state, his diet, other drugs he may be taking, habits with respect to alcohol, individual tolerances, cooperative ability, and the clinician's experience with the drug.

The dangers of hemorrhage are the principle complications of long term anticoagulant therapy. Minor hemorrhages are to be expected when an ambulatory patient is taking an anticoagulant; examples are easy bruising, slight bleeding of the gums and nose, and microscopic hematuria. Anticoagulants need not be stopped when the bleeding is slight and the prothrombin time low. Massive hemorrhage is uncommon, and when it occurs it is usually from the gastrointestinal tract, genitourinary tract, or cerebral hemorrhage. Although hemorrhage can occur and has been reported from almost any organ in the body, since the advent

of Vitamin K_1 preparations, the possibility of severe hemorrhage is becoming less and less an objection to this therapy.

It has been variously reported that 1/3 to 1/2 of the thromboembolic complications of long term anticoagulant therapy are fatal. The majority of thromboembolic complications are recurrent myocardial infarction, pulmonary emboli, peripheral emboli and phlebothrombosis. In approximately half the cases the prothrombin time was 2 to 2 1/2 times the control where it should be for proper effectiveness of long term therapy.

In withdrawing a patient from anticoagulant therapy it should be done slowly because thrombosis has occurred in some instances when the drug has been withdrawn suddenly.

The length of time a patient should be maintained on long term anticoagulant therapy varies greatly with different writers, from 6 to 12 months to the balance of the patient's life. But the clinician should decide this on an individual basis.

In reviewing the results of long term anticoagulant therapy as reported in the literature, the interpretation is made difficult because the investigators use different methods of expressing their results. But regardless of this difficulty all reports are quite favorable to long term therapy. Even the investigators having the poorest results report that the patient on anticoagulant has a

3:1 better chance of not having a recurrent myocardial infarction than the patient who is not receiving anticoagulant. The results of various investigators are quite variable from the lowest of 3 to 1, to the highest of 9 to 1 less recurrent thromboembolic complications. The principal criticism of a large number of investigators is the lack of a proper control series so that their results are based mainly on clinical results. But as time goes on, there should be many larger and better control series such as the one reported by Nichol (1) in 1958. This should further confirm the favorable reports on long term anticoagulant therapy.

CONCLUSIONS

In evaluating the favorable statistical data on long term anticoagulant therapy it must be stressed that the natural cause of coronary disease with all its variables, including environmental and emotional factors, makes the statistics in this condition difficult to obtain and interpret. Also the various investigators use different methods to express their findings, thus precluding any comparison of results obtained by different workers.

Regardless of these difficulties, the evidence appears to be overwhelming that long term anticoagulant therapy favorably affects the grave prognosis following myocardial infarction. This form of treatment has been particularly effective in the group with recurrent infarcts.

Admittedly, it has not been proved that recurrent attacks of coronary thrombosis have been prevented. But Nichol, a clinician, with many years of experience in the field aptly states, "As a clinician with many years of experience prior to the use of anticoagulants in coronary artery disease, I am very impressed with the low mortality in patients on long term anticoagulant therapy over the past 10 years." (1)

The incidence of acute myocardial infarction among patients discontinuing therapy is high, the mortality rate of those having infarcts being 44%.

A cooperative patient, a dependable laboratory and a physician with an adequate knowledge of administering anticoagulants are essential for the success of the treatment. Warfarin appears to be the drug of choice in long term treatment.

Bleeding episodes are an undesirable feature that is less a hazard to the patient with coronary disease than the risk of the disease itself. Major bleeding episodes occur infrequently and can be successfully handled by administering Vitamin K_1 and blood transfusions if needed.

Properly controlled long term anticoagulant therapy is relatively safe and deaths which have occurred while the patient is on this therapy are seldom related to the anticoagulant.

I strongly feel that long term anticoagulant therapy is a definite step towards lengthening life and productivity of a large number of people.

BIBLIOGRAPHY

1. Nichol, E. S., et al., Long Term Anticoagulant Therapy in Coronary Atherosclerosis, Am. Heart J. 55:142 (Jan.) 1958.

2. Jordan, F. L. J. and Presst, K., The Problem of Interpretation of Results Obtained by Long Term Anticoagulant Treatment in Myocardial Infarction, Acta Scand. Med. 162:137, 1958.

3. Editorial, Anticoagulants: A Cooperative Effort, J.A.M.A. 169:982 (March 28) 1959.

4. Putnam, T. J., et al., Results of Treatment of Multiple Sclerosis with Dicoumarin, Arch. Neurol. Psychiat. 57:1, 1947.

5. Nichol, E. S., and Fassett, D. W., An Attempt to Forestall Acute Coronary Artery Thrombosis, South. Med. J. 40:631, 1947.

6. Peters, H. R., Geyther, J. R., and Brambel, C. E., Dicumarol in Acute Coronary Thrombosis, J.A.M.A. 130: 39, 1946.

7. Wright, I. S. and Foley, W. T., Use of anticoagulant in the treatment of heart disease, with special reference to coronary thrombosis, rheumatic heart disease with thromboembolic complications and subacute bacterial endocarditis, Am. J. Med. 3:710, 1947.

8. Allen, E. V., et al., The Use of Dicumarol as an Anticoagulant; Experience in 2,307 Cases, Ann. Int. Med. 371:381, 1947.

9. Owren, P. A., Long Term Therapy in Cardiovascular Diseases, Acta Med. Scand. 287:46, 1953.

10. _____, Permanent AC Therapy in Cardiovascular Disease, Northwest Med., pp. 298-307, March 1957.

11. Sprague, H. B. and Jacobsen, R. P., Ambulatory Treatment with Dicumarol, Med. Clin. No. Am. 32: 1308, 1948.

12. Olwin, J. H., Control of Dicumarol Therapy, Am. J. Med. Sc. 217:427, 1949.

13. Askey, J. M. and Cherry, C. B., Continuous Anticoagulant Therapy, J.A.M.A. 144:97, 1950.

14. Cosgriff, S. W., Prophylaxis of Recurrent Embolism of Intracardial Origin, J.A.M.A. 143:870, 1950.

15. _____, Chronic Anticoagulant Therapy in Recurrent Embolism of Cardiac Origin, Ann. Int. Med. 38:278, 1953.

16. Shapiro, S., Long Term Anticoagulant Therapy, Med. Clin. No. Am. 37:659, 1953.

17. Brotman, I., Anticoagulants in Myocardial Infarction, Acute and Long Term Therapy, Am. J. Cardiology, 1:260, 1958.

18. Estes, J. E., Long Term Anticoagulant Therapy, Postgrad. Med. 22:323 (Oct.) 1957.

19. Wright, I. S., et al., Long Term Anticoagulation Therapy, Circulation 9:748 (May) 1954.

20. Meyer, O. O., Use of Anticoagulants in the Treatment of Coronary Artery Disease, Postgrad. Med. 24:110, 1958.

21. Toohey, M., Long Term AC Therapy for Coronary Thrombosis, Brit. Med. J. 5093:473, (Aug.) 1958.

22. Loughridge, W. M., Long Term AC Treatment of Coronary Thrombosis in General Practice, Brit. Med. J. 5146: 217 (Aug.) 1959.

23. Olwin, J. H. and Koppel, J. L., Practical Aspects of Long Term Anticoagulant Therapy, Arch. Int. Med. 100: 842 (Nov.) 1957.

24. Pastor, B. H. and Tetrealt, A. F., Agranulocytosis and Scarlatiniform Eruptions due to Phenindione, J.A.M.A. 161:873 (June 30) 1956.

25. Ager, J.A.M. and Ingram, G.I.C., Agranulocytosis, during Phenindione Therapy, Brit. Med. J. 5027:1102, (May) 1957.

26. Olwin, J. H., et al., Choice and Control of Anticoagulant Drugs, Geriatrics 13:773 (Dec.) 1958.

27. Wright, I. S., Present Status of Anticoagulant Therapy in the Treatment of Myocardial Infarction; the use and misuse of anticoagulants; an evaluation of new anticoagulants, their indications and dosage, Ann. Int. Med. 43:942 (Nov.) 1955.

28. Putnam, W., Long Term Anticoagulant Therapy, GP 36:79, 1958.

29. Sise, H. S., et al., Plasma Thromboplastin Component (PTC) Deficiency Produced by Prolonged Administration of Prothrombopenic Anticoagulants, Proc. Soc. Exper. Biol. & Med. 89:81, 1955.

30. Toohey, M., Comparison of Quick's, Owren's, and Ware's Techniques for the Control of Anticoagulant Therapy, J. Clin. Path. 11:56 (Jan.) 1958.

31. Jolly, A.T.H., Long Term Anticoagulant Treatment, Med. J. Australia 1:609, 1958.

32. Tanzi, F. and Van Ness, A. L., Long Term Anticoagulant Therapy of the Ambulatory Patient Following Myocardial Infarction, Med. Clin. No. Am., pp. 25-31, Jan. 1957.

33. Tulloch, J. and Wright, I., Long Term Anticoagulant Experiences; Further Experiences, Circulation 9:823, (June) 1954.

34. Goodman, H. L., Acute Non-specific Pericarditis with Cardiac Tamponade, Ann. Int. Med. 48:406 (Feb.) 1958.

35. Chokas, W. V., Bilateral Adrenal Hemorrhage Complicating Dicumarol Therapy, Am. J. Med. 454:460 (March)1958.

36. Cloward, R. B. and Yechl, E. T., Spontaneous Intraspinal Hemorrhage and Paraplegia Complicating Dicumarol Therapy, Neurology 5:600 (Aug.) 1955.

37. Waldron, B. R., et al., Myocardial Rupture and Hemopericardium Assodated with AC Therapy, New England J. Med. 251:892 (Nov.) 1954.

38. Ziffer, A. M., et al., Profound Bleeding after Dental Extractions during Dicumarol Therapy, New England J. Med. 351:3 (Feb.) 1957.

39. Ensor, R. and Peters, H. R., Long Term AC Therapy in Coronary Disease, J.A.M.A. 169:914 (Feb.) 1959.

40. Borg, J. F., The Value of Prolonged Anticoagulant Therapy, Minn. Med. J. 39:37 (Jan.) 1956.

41. Stephans, M. D. Jr., AC Therapy in Private Practice, Circulation 9:682 (May) 1959.

42. Nichol, E. S., et al., Symposium on Efficiency of New Drugs; AC in Coronary Heart Disease, Med. Clin. No. Am. 38:399 (March) 1954.

43. Foley, W. T. et al., Further Experiences with Long Term Anticoagulant Therapy, Arch. Int. Med. 95:497 (April) 1955.

44. Suzman, M. M., et al., Evaluation of Effects of Continuous Long Term AC Therapy on the Prognosis of Myocardial Infarction; Report of 82 Cases, Circulation 12:338 (Sept.) 1955.

45. Keyes, J. W., et al., Survival Rates after Acute Myocardial Infarction with Long Term Anticoagulant Therapy, Circulation 14:254 (Aug.) 1956.

46. Manchester, B., Prevention of Myocardial Infarction, Arch. Int. Med. 100:959 (Dec.) 1959.

47. Bjerkelund, B. J., The Effect of Long Term Treatment with Dicoumarol in Myocardial Infarction, Acta Med. Scand. 330:1, 1957.

48. Bengtsen, K. K. and Aspenstrom, C., Preliminary Report on Long Term Treatment of Cardiosclerosis with Dicumarol, Acta Med. Scand. 157:217, 1957.

49. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council of England. An Assessment of Long Term Anticoagulant Administration after Cardiac Infarction, Brit. Med. J. 5125:803 (March) 1959.

50. Tandowsky, R. M., Phenylindandione in Therapy of Coronary Artery Disease, Study of its Long Term Use in Ambulatory Patients, Am. J. Cardiology 3:551 (April) 1959.