Analytical Review

Anticoagulant Therapy

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THE VALUE of anticoagulant drugs in thrombotic disease is still disputed despite innumerable reports and reviews and despite the fact that these drugs have been used for close on 30 years.1-5 Our object in writing this report is to highlight some of the issues where there is major controversy, to indicate theoretical and practical aspects which appear to us to be of major importance, and to define the current status of the practice of anticoagulant therapy in clinical medicine.

THEORETICAL AND LABORATORY ASPECTS

Anticoagulant Drugs and Blood Coagulation

Anticoagulant drugs appear to have a rational basis for use. It has been postulated that intravascular blood coagulation occurs constantly and that fibrin is continually being formed and being deposited on the vascular endothelium, and just as continuously being removed by fibrinolysis.6,7 It is claimed that there is a “dynamic equilibrium” between the intrinsic clotting system and the fibrinolytic system.8 Consequently, if there were “imbalance” of this equilibrium, one approach to treatment might be by use of anticoagulant drugs. It is by no means certain that there is such an equilibrium or that intravascular coagulation is a continuous process.9 Even if it were so, there is evidence that the products of coagulation might be removed, at least in part, by the reticuloendothelial system.10 Consequently, this premise for use of anticoagulant drugs might be questioned.

Hypercoagulability of the blood may be important in the genesis of intravascular clot formation, and be a process amenable to therapy with anticoagulant drugs. It is not clear how one should define this suggested hypercoagulability, but many authors have equated it with accelerated blood coagulation as judged by a clotting test system or by elevation of a blood coagulation factor above normal. The former is difficult to recognize and both are of doubtful validity with regard to hypercoagulability. Hypercoagulability, occurring locally, appears more likely with the resulting products being so diluted in the total blood volume as to be unrecognizable in blood collected from a distant vein; alternatively, if the process were sufficiently diffuse, it could consume labile clotting factors, cause defibrination and pro-

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duce a generalized hypocoagulable state. Such states occur under a variety of circumstances (injury and shock, toxemia of pregnancy, disseminated cancer, etc.) and some of these can be treated by heparin. But there is, at present, little acceptable evidence that spontaneous persisting generalized hypercoagulability occurs and causes a thrombotic state in man.

Blood Clots and Thrombus Formation

At this point it is necessary to draw an important distinction between the processes of blood coagulation and those of thrombus formation. It has been known for a century or more that there is a very important difference between a blood clot and a thrombus and as long ago as 1899 Welch complained about the "old and still common conception that a thrombus is essentially a blood coagulum." The same misconception is common today. Briefly stated, a clot forms in static blood and consists of red cells, white cells and platelets randomly dispersed in a fibrin network. A thrombus forms in moving blood and is composed of masses of agglutinated platelets, some red cells, white cells and a little fibrin. The distinction is not absolute since intermediate grades exist. An arterial thrombus usually has more abundant platelet material than does a venous thrombus; the latter may have a white head of platelet material attached to the vessel wall with a much larger "red tail" (blood clot) streaming away in the direction of the blood flow. Anti-coagulant drugs are not antithrombotic, thus their therapeutic efficacy might be greater in the "clot" portion of the intravascular material.

It is not clear why thrombi start to form in blood vessels nor is the process of spontaneous thrombus formation easy to study under experimental conditions. Recent work on the formation of the hemostatic plug which follows injury to a small blood vessel may be pertinent to this discussion. Following trauma to a vessel, platelets adhere to the injured site, adenosine diphosphate (ADP) is released and this leads to platelet aggregation by increasing platelet adhesiveness without further release of ADP. (At this stage the process is still apparently, partially or totally reversible and some of the platelet masses may get swept away in the blood stream.) Next, thrombin release from the process of blood coagulation causes platelet coalescence and initiates further release of ADP from the platelets. It is only at this point that the first strands of fibrin are seen on or near the surface and probably not in the depths of the thrombus. Thus, factors affecting the accumulation of platelets at a local site are of prime importance in the process of thrombus formation. Blood coagulation becomes important only at a later stage and causes consolidation of the thrombus and perhaps its extension. When a vessel wall is injured with a minimal stimulus, no spontaneous thrombi occur. If ADP is then applied locally, thrombus formation can be induced. If systemic "hypercoagulability" is produced by the injection of Russell Viper Venom or "product 1" thrombus formation at this local site is not augmented.

Rokitansky, over 100 years ago, first enunciated the concept that atheromatous plaques resulted from the incorporation of fibrin encrustations into the intimal layer of the vessel. This idea lay dormant for many years until it
was resurrected by Clark, Graef and Chasis\textsuperscript{24} and later by Duguid.\textsuperscript{29} Atheroma, in this view, results from recurrent thrombosis. Recently,\textsuperscript{36} Pickering has “modernized” this theory by suggesting that platelet-leukocyte-fibrin thrombi, and not fibrin become incorporated in the vascular endothelium. This theory has received considerable support\textsuperscript{31} but it is certainly not universally accepted. Nor should one necessarily expect much benefit from anticoagulant drugs in prophylaxis of this disease. They might prevent some fibrin deposits but they should not be expected to prevent platelet thrombus formation.

In sufficient dosage both heparin and bis-hydroxycoumarin (Dicumarol\textsuperscript{®}) are anticoagulant. Heparin in very large doses has been said to prevent thrombus formation and as long ago as 1939 a similar claim was made for Dicumarol.\textsuperscript{32,33} There is however, much conflicting evidence too abundant to review here. Although Dicumarol therapy in man decreases platelet adhesiveness,\textsuperscript{34} Zucker\textsuperscript{4} found that very large doses of either heparin or Dicumarol were required before hemostasis was impaired. Thrombin, in concentrations not apparently able to convert fibrinogen to fibrin, can clump platelets.\textsuperscript{35} Platelets will clump in the presence of very little thrombin and in order to prevent the appearance of such small quantities one needs to achieve a very marked depression of clotting factors. In the (injured) hamster cheek pouch fibrin formation may be depressed by anticoagulants but platelet clumping is more difficult to prevent.\textsuperscript{36} Stasis clots can be induced in dogs infused with normal serum. These can still be produced if the donor and the recipient dogs are given Dicumarol for a short period of time. Fewer clots are produced if the donor dogs receive Dicumarol for a longer time. Heparin therapy is also more successful in preventing such clots\textsuperscript{37,38} than is short-term Dicumarol therapy. However, heparin, in dosage far in excess of that used therapeutically in man, is ineffective in prevention of thrombi in mechanically injured rabbit cortical vessels\textsuperscript{25} or the hamster cheek pouch,\textsuperscript{36} although it does have a moderate effect in reducing the size of the thrombi.\textsuperscript{25}

The dose of anticoagulant drug is very important since small (inadequate) doses of heparin or Dicumarol may even be thrombogenic. More thrombi occur in rats given small doses of Dicumarol or heparin than in rats given no anticoagulant drugs when formalin is applied topically to veins, whereas more adequate doses of either reduce the incidence of thrombus formation.\textsuperscript{39} Similar findings have been noted in the amount of thrombus formation in pigs with extracorporeal shunts.\textsuperscript{40} Using platelet survival as the parameter it is seen that adequate doses of either Dicumarol\textsuperscript{41} or heparin prolong platelet survival, whereas inadequate amounts of Dicumarol have the opposite effect and actually increase platelet adhesiveness and shorten platelet survival.\textsuperscript{42,44} Relatively enormous doses of heparin or Dicumarol are needed to reduce platelet adhesiveness significantly, to diminish platelet turnover or reduce thrombus formation.\textsuperscript{42}

Platelet adhesiveness\textsuperscript{45} is said to be increased in patients with ischemic heart disease and by fat containing meals in patients with the disease but not in controls.\textsuperscript{46} It is claimed, but as yet not confirmed, that heparin, given
twice weekly in small doses, normalizes this increased platelet adhesiveness. Many would agree with Owren that while platelet adhesiveness has been said to be lessened by heparin, the doses which can be utilized clinically are unlikely to alter significantly platelet adhesiveness as measured in vitro. Furthermore, "usual doses" of oral anticoagulants, or deliberately small doses, may increase the adhesive index during the first 72 hours of treatment.

Since the aggregation and coalescence of platelets is important in the formation of thrombi, and since ADP release participates in this phenomenon it is pertinent to consider the effects of anticoagulants and other drugs in the presence of ADP. Studies in vitro on platelet aggregation produced by ADP have shown this is, within certain limits, almost linear to the log of the concentration of the dose. More than 180 units of heparin per ml. of plasma, an enormous dose, is required to decrease platelet adhesiveness produced by 0.4 µg. of ADP. Furthermore, it has been shown that platelet clumping can also be produced by adenosine triphosphate, 5-hydroxytryptamine, adrenaline and noradrenaline and other substances. Enzyme inhibitors (e.g., sodium-azide, fluoracetate, potassium cyanide, etc.) in concentration capable of blocking enzymic processes in muscle cells, have no effect on platelet agglutination in vitro.

The antiadrenaline compound phentolamine inhibits platelet aggregation but another antiadrenaline compound (dibenzyline) and some antiserotonins, do not, except at high concentrations. The plasma itself has the capacity to destroy or inactivate ADP. If a reasonable amount of ADP is infused intravenously it does not cause massive and persistent platelet aggregation. The fall in platelet count produced in man by the intravenous injection of ADP sufficient to produce plasma concentration up to 1 x 10^{-9}M may be due merely to transient platelet sequestration in the splanchnic or pulmonary circulation. ADP needs to be locally applied, close to the site of injury, in order to augment thrombus growth. Breakdown products of ADP like adenosine monophosphate and adenosine as well as related substances like 2-chloroadenosine do inhibit platelet aggregation as well as the formation of thrombi in injured cortical vessels of rabbits.

Enough has been said to indicate that considerable doubt exists regarding the theoretical basis on which anticoagulant drugs as currently used might be expected to be beneficial in human thrombotic states. The conditions favoring their action are present more in veins than in arteries, they may perhaps have a small effect in preventing the formation and inhibiting the growth of true thrombi and have some effect on the blood clot which forms in association with these thrombi. Most of the evidence indicates that although we are able to achieve adequate anticoagulant therapy, we fail to provide substantial antithrombotic effect. Perhaps our search for antithrombotic agents should be directed more towards those which inhibit platelet aggregation and away from those which prevent blood clotting; such trials have already begun.

Anticoagulant Administration: Dosage and Control

One should next consider which drugs should be used and how the treat-
ment should be controlled. Heparin and one of the coumarin or inandione
drugs remain the drugs of choice. Which of the latter to use is largely a matter
of individual preference and similar results can be obtained with a variety of
such drugs. The most commonly used drugs are Dicumarol, warfarin sodium
and phenindione. The last mentioned is widely used overseas but it has a high
incidence of toxic effects (skin rashes, leukopenia, agranulocytosis, hepatitis).
These can be anticipated and the drug discontinued before harm is done. A
“therapeutic level” is readily achieved and maintained and phenindione has
proved to be at least as satisfactory as any other similar drug. In our view,
however, warfarin sodium is the drug of choice; the action is rapid, the drug
can be given parenterally, and a stable level is easily achieved. In this respect
it is simpler to use than Dicumarol and the therapeutic range more easily
maintained. Possibly it is absorbed more completely. Numerous other
drugs of similar type have been used “successfully.” It seems to us that the
important thing is to know how to use one drug and to use it intelligently.
The dose of the drug for an individual patient seldom varies significantly from
week-to-week. Fluctuations in prothrombin time are more likely to be due
to laboratory variation or to negligence of the patient in taking prescribed
medication. We advise our patients to set aside a week’s supply of the drug
and take these pills during the week; pills left over at the end of the week
should be swallowed! We try to alter the dose by no more than a half or one
pill a week. In this way many of our patients have not altered their dosage
over long periods of time. The physical status of the patient, however, can
have an effect on drug requirements as can many other things. Other medica-
tion, such as salicylates and antibiotics, can reduce the dosage requirements.
Of recent interest has been the realization that anabolic steroids used to re-
duce blood lipids, can so reduce anticoagulant requirements that the “usual”
dose may become dangerous overdosage. In addition, we have recently
noted that male subjects require a larger mean dose than do females, and
we have confirmed Seaman’s recent report that the dose requirements di-
minish with advancing age (fig. 1).
What is the optimum therapeutic level of anticoagulation which should
be maintained? Despite a great deal of clinical pontification no one really
knows the answer to this most important question. On general principles
one could argue that, unless there were good reasons opposing the concept,
the “correct” dose would be the greatest one could administer with safety.
Sevitt and Innes concluded from their clinical study that quite severe de-
pression of prothrombin complex was necessary for prevention of venous
thrombi, a dosage schedule which was associated with a significant incidence
of bleeding. This viewpoint has not gone undisputed. Others found no good correlation between the number of deaths from acute myocardial
infarction and the adequacy of therapeutic level achieved.
The laboratory test used for control of dosage is of paramount importance
but here, too, there are innumerable “recommended” methods. As one of us
pointed out many years ago it is not possible to equate different methods of
control or even the same methods used in different laboratories. The “Quick”
one-stage method and the two tests devised by Owren (P and P and the
Fig. 1.—Anticoagulant dosage related to age and sex of patients on long-term anticoagulant therapy. The ordinate ("cumulative frequency per cent") indicates the percentage of patients requiring either the dose of phenindione shown on the abscissa or less than that dosage. The lower panel demonstrates that females require less phenindione than do males of comparable age \( (p < 0.01) \) and both panels reflect the diminished requirement after age 61 in males \( (p < 0.02) \) and females \( (p < 0.07) \).

Thrombotest\(^{23,74}\) are the ones most widely used. The one-stage method is simple, reproducible and cheap. So widely do the results differ depending on the thromboplastin used and the method of expression of results,\(^{75}\) that we have long advocated each laboratory determine its own limits of safety. With acetone dried human brain thromboplastin we have found a prothrombin time which is 1.8–2.5 times that of a normal control plasma to be the lowest levels we care to use. This corresponds to 2.4–3.0 times the control time if saline extracted human brain is used. If rabbit brain thromboplastin or other commercial thromboplastins are used these may prove to be dangerous levels of therapy and it may not be safe to prolong the prothrombin time beyond 1.5–2.0 times the control time (fig. 2).\(^{76}\) Dilution curves provide only another variable and contribute little to safer control. The P and P and the thrombotest methods lauded because they provide smoother and safer control, are time consuming, expensive, and at the "recommended" therapeutic levels, provide less intensive therapy. At our usual therapeutic level of 1.8–2.5 times the control time, we found levels of less than 5 per cent when the blood from
Fig. 2.—Prothrombin index as judged by different thromboplastins and by thrombotest with the same patient’s specimens being used in the 3 tests. The commercial thromboplastin indicates a lesser level of prothrombin complex depression than does the human brain thromboplastin, whereas many of the thrombotest readings are below the usually recommended therapeutic range (indicated by bars). The prothrombin index is calculated:

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\frac{\text{Prothrombin time of control}}{\text{Prothrombin time of patient}} \times 100
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these patients was evaluated with thrombotest (fig. 2). This is well below Owren’s recommended therapeutic level.\textsuperscript{75,76} Small wonder therefore that bleeding is seldom encountered if thrombotest is used to control the level of therapy. Much has been made of the sensitivity of thrombotest to depressed levels of factor IX. This is true when other factors involved in the intrinsic coagulation system are also depressed\textsuperscript{76} but not otherwise.\textsuperscript{77} However, this fact does not seem to be of much importance in practice. The value of thrombotest remains disputed\textsuperscript{74,81} and we do not recommend its use. In France, Soulier\textsuperscript{82} uses the heparin tolerance test for control of therapy; his results are not demonstrably superior or inferior to those of others. The results of this test seem to bear little relation to those obtained with the use of the one-stage Quick test. Yet, this method, as well as many others used to control therapy, has been claimed to give “good” clinical results from the point of view of controlling thrombosis and of preventing excessive bleeding. Other methods advocated are the so-called standard clotting time test\textsuperscript{83} and methods using TAMe hydrolysis.\textsuperscript{84,85} These appear to us to be methods of considerable theoretical interest but involve a great deal of effort and fail to achieve comparable, let alone superior, results. We do not advocate their use.
Heparin is used mainly for rapid induction of treatment since an intravenous injection has an immediate effect. Therapy is generally continued either intravenously or by deep subcutaneous injection ("in the fat") for the next 48–72 hours at which time the orally active drugs will have achieved a "therapeutic" level. Supplementary oral anticoagulant therapy with heparin is not universally considered of value.86 Some advocate heparin daily, or once or twice a week, for prolonged periods of time.87 It is even claimed that the therapeutic efficacy is not necessarily correlated with its anticoagulant effect. The continuous use of heparin is associated with considerable morbidity in the way of bruising and bleeding and it is of doubtful benefit. We would prefer to await the results of adequate double-blind studies before recommending its use.

**Clinical Aspects**

The results of clinical trials must, in the final analysis, form the basis for estimating the value of anticoagulant therapy in thromboembolic conditions. None of the completed trials has met the rigid requirements of an ideal clinical trial as described by Douglas:97 double-blind technic, random allocation of subjects into treated and control groups, determination of suitability for anticoagulant therapy prior to allocation into treated and control groups, identical therapeutic regimen in both groups, except for the anticoagulant drug, and objective criteria such as death rate for determining the value of the therapy.

**Deep Vein Thrombosis and Pulmonary Emboli**

Although most of the published trials are open to criticism because the control groups have not been comparable to the treated groups, there seems to be no doubt that anticoagulant therapy is of decisive value in the treatment of deep vein thrombotic disorders.88–94 Mortality, pulmonary emboli, and post-thrombotic sequelae in the lower extremities are all impressively reduced. When the thrombotic disorder involves superficial varicose veins anticoagulant therapy is usually not indicated unless there is a question of deep vein involvement.

Barritt and Jordan,95 in a well designed controlled trial, demonstrated that anticoagulant therapy is of pronounced value even when started after pulmonary embolism has occurred, whether or not deep vein thrombosis is apparent. In 19 control subjects there were 5 deaths from pulmonary emboli and 5 nonfatal recurrences, while in 16 treated patients there were no further pulmonary emboli.

In bedridden patients, the frequency of deep vein thrombosis96,97 and pulmonary embolism98–100 has prompted the investigation of prophylaxis of these disorders with anticoagulant therapy. The common factor in the development of deep vein thrombosis is venous stasis of the lower limbs and bedrest is the principal contributing factor to such stasis. The specific reason for the bedrest is of only secondary importance. The risk of deep vein thrombosis and pulmonary embolism increases with age and duration of bedrest,101 though the duration of bedrest is probably the more important factor.102 Clinico-pathologic studies reveal that deep vein thrombosis occurs without symptoms
in the majority of patients even when under careful observation and most pulmonary emboli occur unheralded by signs or symptoms of deep vein thrombosis. The distressing frequency of silent deep vein thrombosis and subsequent unheralded pulmonary embolism emphasize that prophylaxis rather than treatment is the most beneficial therapeutic approach. This has been demonstrated following a variety of operative procedures with the treated subjects having an incidence of thromboembolism only one-fifth that of the control group. Similar results have been found in the puerperium, after obstetric and gynecologic surgery, and following fractured hip in elderly patients. In the latter trial there were only 7 thromboembolic occurrences in 150 treated patients compared to 59 such episodes in 150 control subjects. It is worth noting that the fractures were pinned or nailed while patients were receiving anticoagulants without significant hemorrhage. Similar observations have been made in other types of surgery. If early mobilization of the patient is possible then anticoagulant therapy may not be required for reducing thromboembolism.

In patients with congestive heart failure prophylactic use of anticoagulant drugs has been found to reduce the incidence of deep vein thrombosis and pulmonary embolism. It is likely that prompt treatment of congestive failure and early ambulation would also reduce these complications. Despite the apparent value of prophylactic anticoagulant therapy in patients confined to bed for a variety of conditions such prophylaxis is not extensively utilized; elastic bandages and early mobilization are more often used. Wilkins and Stanton found the expected incidence of fatal pulmonary embolism reduced by about half when elastic stockings were routinely used in medical, surgical, and obstetrical patients.

In practice it is difficult to use anticoagulant drugs prophylactically in every injured, puerperal or postoperative patient, but certain recognizable "high risk" categories of patients should be considered for prophylactic anticoagulant therapy.

**Conclusion:** The evidence overwhelmingly indicates that anticoagulant therapy is of value in the prevention and treatment of deep vein thrombosis and pulmonary embolism.

**Peripheral Emboli**

In patients with rheumatic mitral stenosis and atrial fibrillation clinically recognizable embolic phenomena, commonly multiple, have been noted in to per cent of those not treated with anticoagulants. Recurrent emboli usually occur within 1 year. Intracardiac thrombi have been found in per cent of necropsy examinations in patients with mitral stenosis, the greatest incidence being in those patients with atrial fibrillation and advanced age. embolization occurring commonly.

The incidence of recurrent emboli has been strikingly reduced by anticoagulant therapy. McDevitt and her colleagues studied 100 patients during 2,542 patient months without anticoagulant therapy and observed 229 episodes of thromboembolism, including 67 which were cerebral. In 2,291 patient months in which anticoagulant therapy was used only 20 such epi-
sodes occurred, 5 being cerebral. Cosgriff,126 Owren127 and others128-130 have observed similar results. The question of how promptly anticoagulant therapy should be started after cerebral embolus will be dealt with later. Fewer thromboembolic complications have also been observed in patients with atrial fibrillation following acute myocardial infarction when anticoagulant drugs have been used.69

Conclusion: Despite the absence of satisfactory controlled trials the evidence indicates that anticoagulant therapy is of definite value in reducing the incidence of peripheral emboli.

Cerebrovascular Disease

Cerebrovascular disease is a multifaceted disorder with each facet requiring separate evaluation. The clinical categories elaborated by Shaw131 will be utilized in this discussion.

Transient Ischemic Attacks: These are distinct attacks of neurologic dysfunction of short duration and usually entirely reversible. Attacks may cease spontaneously or progress to cerebral infarction. The infrequent occurrence of this disorder and the difficulty in being certain of the diagnosis have presented obstacles to the collection of an adequate series of patients necessary for a properly controlled clinical trial.

Striking reduction of transient ischemic attacks and subsequent cerebral infarction have been observed in patients receiving anticoagulant therapy.132-135 The controlled cooperative study carried out at 9 Veterans’ Administration hospitals136 also showed that anticoagulant therapy reduced the number of cerebral ischemic attacks. In 22 treated patients observed for an average period of 9.3 months there was only one ischemic episode, while in 15 control subjects observed for an average of 12.8 months there were 8 such episodes. During the period of observation only one of these 37 patients with ischemic attacks subsequently infarcted and none died. The national cooperative controlled study137 conducted in 7 clinical centers was composed of 443 patients and included 44 patients with transient ischemic attacks, 20 in the control group and 24 in the treated group. There were 547 ischemic episodes during 410 patient months in the control group and only 25 during 439 patient months in the treated group throughout the 42 month period of the trial. One treated and 4 control subjects ultimately infarcted, and 5 treated and 2 control subjects died. Patients with carotid and vertebrobasilar insufficiency syndromes responded similarly. Despite this reduction in transient ischemic attacks with anticoagulant therapy in these cooperative studies, the mortality was not reduced. Bradshaw and McQuaid observed that the prognosis in their untreated patients with vertebrobasilar insufficiency was not as ominous as has been generally thought.138 The need for additional properly designed controlled trials to evaluate anticoagulant therapy in this disorder has recently been emphasized.139

Progressively Evolving Strokes (Thrombosis or Stroke-in-Evolution): This disorder presents clinically with a progressing neurologic deficit whose course may be measured in hours or days. These strokes may evolve in a step-wise manner or in an unremitting gradual fashion. It is often impossible to dis-
tistinguish at any given moment between the patient whose lesion is going to progress and the one whose lesion has reached its maximum. Anticoagulant treatment in the former might be helpful while treatment in the latter might be harmful. Carter in a well designed controlled study found that anticoagulant therapy benefited patients with incomplete and progressing strokes. Seventeen (77 per cent) of 22 treated patients recovered or improved and only 10 (50 per cent) of 20 control patients recovered or improved (P < 0.05). There were 4 (20 per cent) deaths in the control group and only one (5 per cent) in the treated group. There were 18 patients in the control group with completed strokes of whom 9 (50 per cent) recovered or improved and 3 (16 per cent) died, compared with 16 patients in the treated group of whom 7 (44 per cent) recovered or improved and 2 (13 per cent) died. Anticoagulant therapy obviously did not benefit those patients with completed strokes. Reduction in the death rate with anticoagulant therapy may have been related to prevention of pulmonary infarction since 3 of 5 autopsied control patients died from this complication while none of 3 autopsied treated patients were so afflicted. In the national cooperative study anticoagulant therapy did not alter the mortality in the progressively evolving stroke but progression of the neurologic deficits and subsequent infarctions were reduced. The clinical studies of Millikan, Siekert and Whisnant and Fisher also showed anticoagulant therapy to be beneficial, but there were no true control groups in these trials. The evidence is suggestive that anticoagulant therapy might be helpful in patients with progressively evolving strokes providing infarction has not occurred.

**Completed Stroke (Cerebral Thrombosis or Infarction):** This lesion represents the great majority of clinically manifest cerebrovascular disorders. It is the neurologic lesion in which the clinical deficit is no longer extending. Marshall and Shaw studied the use of anticoagulants promptly after nonembolic and presumably nonhemorrhagic cerebrovascular accidents in a controlled trial in which the patients were treated for 21 days and observed for 6 months. All patients had angiographic studies. In 26 treated patients there were 6 deaths within the first 6 weeks, 3 from intracerebral hemorrhage, while in 25 control patients there were 3 deaths, one from hemorrhagic infarction. From 6 weeks to 6 months there were 2 additional deaths in the treated group and 4 in the control group. The authors commented that distinguishing between cerebral hemorrhage and cerebral infarction is extremely difficult and the risk of aggravating a misdiagnosed cerebral hemorrhage is ominously present when anticoagulant therapy is used. Hill, Marshall, and Shaw in a well designed controlled long-term trial (20 months) with 71 patients in each group observed 4 deaths from intracerebral hemorrhage and one from hemopericardium in the treated group and no deaths in the control group. Since 3 of the 4 treated patients with intracerebral hemorrhage were hypertensive (diastolic blood pressure more than 110 mm. Hg.) it was decided to continue the trial only in those patients with diastolic blood pressures less than 110 mm. Hg. Omitting the hypertensive patients there were 66 treated and 65 control subjects remaining. Five fatal cerebrovascular accidents, including 3 intracerebral hemorrhages, occurred in the treated
group, whereas only one occurred in the control group. Recurrent nonfatal cerebrovascular accidents were essentially the same in the treated and control groups, including or excluding the hypertensive subjects. The Veterans' Administration\textsuperscript{136} and national\textsuperscript{137} cooperative trials reached similar conclusions. Groch, McDevitt and Wright\textsuperscript{145} in their long-term controlled trial observed a reduction in recurrent thromboembolism and mortality in those treated patients with completed strokes in whom anticoagulant therapy was "properly maintained." They concluded that such therapy "would seem to be indicated only in carefully selected patients." The danger of intracerebral hemorrhage in patients with cerebrovascular disease, especially when hypertension is present, has been emphasized in many studies.\textsuperscript{136, 137, 140, 142-145} Severe hypertension should be considered a contraindication to anticoagulant therapy.

These studies clearly demonstrate anticoagulant therapy does not reduce the mortality nor does it favorably influence the frequency or severity of recurrent nonfatal strokes in patients who have suffered completed, presumably thrombotic, cerebrovascular accidents. On the contrary, the mortality may actually be increased.

Cerebral Embolism (Acute Embolic Infarction): As was previously discussed there is little doubt that anticoagulant therapy is effective in preventing recurrent emboli emanating from the heart some of which may go into cerebral circulation. There is, however, some controversy over when the treatment should be started. Experimental studies by Frazier and associates\textsuperscript{146} demonstrated that anticoagulant therapy failed to protect dogs from cerebral infarcts when homologous blood clots were injected into the internal carotid artery. Wood,\textsuperscript{147} Moyes\textsuperscript{148} and their colleagues found that the extent of hemorrhagic infarction after the injection of vinyl acetate into the cerebral circulation of dogs was greater in dogs receiving anticoagulant therapy. Clinical trials by Carter\textsuperscript{149} and Wells\textsuperscript{150} did not confirm this experimental evidence. These latter trials showed a reduction in mortality when anticoagulant therapy was used promptly after cerebral infarction. In neither trial, however, was the control group entirely comparable to the treated group.

Since hemorrhagic infarction is always a possibility after a cerebral embolus, and since anticoagulant therapy is utilized primarily to prevent future emboli which may occur days to months apart, Millikan's statement\textsuperscript{151} "it appears prudent to wait three to four days before treatment is begun" seems most reasonable.

Conclusion: There is thus a distinct but limited role for anticoagulant therapy in cerebrovascular disease. In patients with transient ischemic attacks and cerebral emboli there is a noteworthy reduction in recurrences when anticoagulant therapy is used. There may also be some benefit from anticoagulants in the treatment of stroke in evolution (progressing stroke), provided established infarction has not occurred since anticoagulant treatment is not helpful in the latter condition.

In patients likely to benefit from anticoagulant therapy the duration such treatment should be maintained has not been established. In the national cooperative study\textsuperscript{137} it was observed that the number of transient ischemic
attacks in the control group was greatest in the first 4 months and, therefore, perhaps 4 to 6 months of therapy would be sufficient for these patients.

**Coronary or Ischemic Heart Disease**

The passage of time and the completion of many clinical trials, rather than clarifying the role of anticoagulant therapy in ischemic heart disease, has actually enhanced the controversy and fortified the arguments of the “anticongulationists” and the “anti-anticongulationists.”

**Angina Pectoris:** There have been but few investigations of the effect of anticoagulant therapy on the morbidity and mortality of patients with angina pectoris. Waaler demonstrated that anticoagulant therapy benefited patients with angina of less than one year’s duration but was of no significant value in those with a longer history. Borchgrevink in a well-designed, controlled clinical trial clearly showed that men without myocardial infarction who had angina pectoris for less than 2 years benefited greatly from long-term intensive anticoagulant therapy. During this 2½-year trial in which each patient was observed for an average of 16 months, one patient died and 2 had myocardial infarction among 74 patients (57 men, 17 women) treated intensively, compared with 7 deaths and 10 myocardial infarctions among 73 (57 men, 16 women) treated moderately. With these results favoring intensive anticoagulant therapy Borchgrevink changed the moderately treated group to intensive therapy and followed all patients for an average of 19 additional months. During this supplementary observation period there were 6 deaths among 65 patients (50 men, 15 women) changed from moderate to intensive therapy (including 2 who died before therapy was intensified) compared with no deaths among 72 patients (55 men, 17 women) maintained on intensive therapy. Combining the results of the 2 observation periods there was only one death among 74 intensively treated patients compared with 13 deaths among 73 patients treated moderately and then intensively, a difference which is highly significant (p < 0.001). Borchgrevink interpreted these results to mean that patients with longstanding angina pectoris (more than 2 years) are not likely to benefit from anticoagulant therapy. The conclusions drawn from this trial apply only to men since there were but 33 women in the trial and only one died. Owren concluded from these results that early therapy “interferes with the natural course of the disease and favors late prognosis.” This conclusion could be questioned since it has been postulated that inadequate anticoagulant therapy may actually be harmful. We would doubt, however, that little treatment is worse than no treatment.

**Conclusion:** Although we have reservations because of the paucity of studies, anticoagulant therapy may be of value in men with angina pectoris, if started early.

**Impending Myocardial Infarction or Acute Coronary Insufficiency:** This is a borderline, dynamic and sometimes ill-defined state between exertional angina and myocardial infarction. Most commonly it presents with intensification of angina of effort and the appearance of angina at rest in a patient with several months to several years of angina pectoris. The pathogenetic mechanisms are thought to be abrupt partial or complete occlusion of a coro-
nary vessel by thrombosis, subintimal hemorrhage, scar or vasospasm without accompanying myocardial infarction.155

Beamish and Storrie156 studied 100 patients with this syndrome. In 15 patients not treated with anticoagulants, there were 14 who suffered infarction, 11 of whom died, while in the 85 patients who received anticoagulants for at least 6 weeks after the diagnosis was made only 2 infarcted and neither died. Wood157 studied 150 patients over a 10-year period. Anticoagulants were given to 100 patients of whom 3 (3 per cent) infarcted within 2 months. Among the 50 patients not treated with anticoagulants 11 (22 per cent) infarcted. The minimal total mortality was 6 (6 per cent) in the group treated with anticoagulants and 15 (30 per cent) in the group not treated. Vakil158 observed 251 patients with preinfarction angina selected over a 10-year period. Excluding 2 patients who died at the onset of the investigation and 7 who were improperly treated, there were 130 patients treated with anticoagulants and 112 not treated. Among the treated patients 33 (25 per cent) infarcted and 9 (7 per cent) died from infarction compared with 55 (49 per cent) who infarcted and 27 (24 per cent) who died from infarction in the untreated group. Other workers have noted similar results. Douglas57 considers the syndrome of impending myocardial infarction “a prime indication for anticoagulant therapy,” and certainly the trials noted support such a claim. It is important to realize, however, that these were not truly controlled trials in that the “control groups” were not randomly selected. Anticoagulant therapy was considered “too essential” in the treatment of this syndrome to deny it to half the patients as would be required in a controlled study.

Master159 in his experience, has found rest to be the only essential aspect of treatment in this syndrome. He does not believe anticoagulant therapy influences the outcome.

Conclusion: On the basis of the existing evidence anticoagulant therapy should probably be utilized in the management of this syndrome, but adequate controlled trials have yet to be done.

Acute Myocardial Infarction, Short-Term Therapy (Therapy during Hospitalization Immediately Following Infarction): The overwhelming majority of trials published show that anticoagulant therapy does reduce the mortality when used during the several weeks following myocardial infarction (table 1).

A properly constituted trial has never been done with anticoagulant therapy in acute myocardial infarction since methods of allocation have not been carried out in a rigidly random fashion. It is possible, therefore, that the distribution of “good risk” and “poor risk” patients has not always been comparable in the treated and control groups. In the extensive trial of the American Heart Association69 conducted in 16 hospitals the allocation into the treated and control groups was determined by the day of admission and not by random distribution. Examination of the results indicates that some nonrandom factors influenced the day of admission since 55.3 per cent of all patients were admitted on odd days (treatment days), a proportion which would be unlikely if only chance factors were operating. In addition,
Table 1.—Anticoagulant Therapy in Acute Myocardial Infarction*

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Control Group</th>
<th>Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Mortality</td>
</tr>
<tr>
<td>Parker and Barker¹⁶⁰</td>
<td>100</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Peters, Doenges and Brambel¹⁶¹</td>
<td>86</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>Greisman and Marcus¹⁶²</td>
<td>100</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>Hilton et al.¹⁶³</td>
<td>38</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Carmichael and Oetting¹⁶⁴</td>
<td>43</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Furman et al.¹⁶⁵</td>
<td>261</td>
<td>105 (40%)</td>
</tr>
<tr>
<td>Zeluff and Field¹⁶⁶</td>
<td>100</td>
<td>40 (40%)</td>
</tr>
<tr>
<td>Bresnick et al.¹⁶⁷</td>
<td>128</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Schilling¹⁶⁸</td>
<td>60</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>Tulloch and Gilchrist¹⁰⁹</td>
<td>84</td>
<td>34 (40%)</td>
</tr>
<tr>
<td>Mullins et al.¹⁷⁰</td>
<td>120</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>Holten¹⁷¹</td>
<td>256</td>
<td>92 (36%)</td>
</tr>
<tr>
<td>Beckwith and Gage¹⁷²</td>
<td>100</td>
<td>28 (28%)</td>
</tr>
<tr>
<td>Feldman et al.¹⁷³</td>
<td>76</td>
<td>23 (30%)</td>
</tr>
<tr>
<td>Rashkoff et al.¹⁷⁴</td>
<td>145</td>
<td>38 (26%)</td>
</tr>
<tr>
<td>Richter, Del Nunzio and Swiller¹⁷⁵</td>
<td>150</td>
<td>50 (33%)</td>
</tr>
<tr>
<td>Loudon, Pease and Cooke¹⁷⁶</td>
<td>125</td>
<td>51 (41%)</td>
</tr>
<tr>
<td>Wright, Marple and Beck⁶⁹</td>
<td>442</td>
<td>103 (23%)</td>
</tr>
<tr>
<td>Manson and Fullerton¹⁷⁷</td>
<td>150</td>
<td>45 (30%)</td>
</tr>
<tr>
<td>McCluskie and Seaton¹⁷⁸</td>
<td>115</td>
<td>45 (39%)</td>
</tr>
<tr>
<td>Hilden et al.¹⁷⁹</td>
<td>429</td>
<td>109 (25%)</td>
</tr>
</tbody>
</table>

Totals 3108 916 (29%) 2835 475 (17%)

*Modified from Douglas⁵⁷ and Wright, Marple and Beck.⁶⁹

patients in the treated group were admitted earlier and a higher proportion of them were private patients. Tulloch and Gilchrist¹⁶⁹ and McCluskie and Seaton¹⁷⁸ determined their treatment and control groups by the section of the hospital to which the patients were admitted. Hilden et al.¹⁷⁹ conducted their trial in 4 medical departments during which time each department used anticoagulant therapy for 2 of the 4 years of trial. As was conceded by Wright and his colleagues⁶⁹ and denied by Hilden and his associates¹⁷⁹ admissions could have been accelerated, delayed or diverted in accordance with the therapeutic beliefs of the referring or admitting physicians.

Despite the shortcomings of these trials the evidence does favor anticoagulant therapy, perhaps by the prevention of thromboembolism. Wright, Marple and Beck⁶⁹ found in their autopsied patients unmistakably fewer mural thrombi and extracardiac emboli in the patients receiving anticoagulant therapy. Tulloch and Gilchrist¹⁶⁹ studied their autopsy material and found pulmonary emboli in 3.4 per cent of the treated patients and 17 per cent of the control subjects. Honey and Truelove¹⁸¹ noted the “almost complete abolition of deaths from pulmonary embolism” with the use of anticoagulant therapy after myocardial infarction. Hilden et al.¹⁷⁹ found pulmonary infarction, embolism or thrombosis in 28 per cent of 92 autopsied patients who did not receive anticoagulant therapy as compared with only 5 per cent of 84 patients who did receive such therapy. In this study mural thrombi were found in 58 per cent of the autopsied control subjects and in only 24 per cent of the
autopsied treated subjects, while the mortality from thromboembolism was 4.0 per cent in the control patients and 1.4 per cent in the treated patients. Hilden and associates found the overall mortality uninfluenced by anticoagulant therapy (23 per cent in treated group and 25 per cent in control group) despite the unmistakably fewer embolic complications in the treated group and reduced mortality in treated older women (28 per cent mortality in treated group and 40 per cent mortality in control group). They concluded that "anticoagulant therapy is not indicated in acute myocardial infarction."

Russek suggests that early ambulation may have as much to do with decreasing thromboembolism as anticoagulant therapy. Russek and Zohman noted an incidence of thromboembolism of only 2.3 per cent and a total mortality of only 3.3 per cent in 1,000 "good risk" patients who did not receive anticoagulant therapy. They suggest using anticoagulant therapy only in those patients with myocardial infarction who have complications which would prolong their period of bedrest or otherwise enhance the likelihood of deep vein thrombosis and pulmonary embolism, so-called "poor risk patients."

It is quite reasonable to expect that anticoagulant therapy would be most beneficial in those patients most likely to acquire thromboembolic complications, but Halpern et al. found that it was necessary to recategorize about one-third of their patients from "good risk" to "poor risk" during the first 48 hours, pointing out the difficulties in deciding who is likely to remain a "good risk" patient.

**Conclusion:** Realizing the deficiencies of all the studies published so far, the evidence still favors the prompt use of anticoagulant therapy after acute myocardial infarction for the period of hospitalization, at least, if only to prevent deep vein thrombosis and pulmonary embolism.

**Myocardial Infarction, Long-Term Therapy:** The evaluation of long-term therapy after myocardial infarction should be based on a review of the well designed controlled clinical trials. Bjerkelund studied 237 patients who received anticoagulant therapy and survived for 1 month after an acute infarction. Long-term anticoagulant therapy was given to 119 patients (average observation time 52 months) and 118 patients served as controls (average observation time 44 months), receiving neither anticoagulant nor placebo therapy. The department to which the patients were admitted determined whether they were to be in the treated or control group. Except for the fact that only the treated group received medication and had blood drawn for the control of therapy, all aspects of treatment of the 2 groups were identical, and though the method of selection of patients for the treated and control groups was not done randomly the 2 groups seemed comparable. The results of the trial are summarized in table 2. The maximum benefits were in the patients under 60 years of age during the first 12 months of treatment. There were 17 recurrent infarctions and 14 deaths during the first 12 months in patients under 60 years of age not receiving anticoagulant therapy, compared with only 2 recurrent infarctions and 3 deaths in the same age group and period of time in the treated patients (p = 0.05). Beyond the first 12 months and in patients age 60 and over the differences were not significant. Anticoagulant therapy was found to be beneficial only for men (table 3); the 56 women in the trial were not benefited.
Table 2.—Bjerkelund’s Trial.\textsuperscript{180} Mortality and Recurrent Infarction

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulant Group (119 patients)</th>
<th>Control Group (118 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>30 (25%)</td>
<td>48 (41%)</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(recurrent infarction, ruptured heart, sudden death, heart failure)</td>
<td>23 (19%)</td>
<td>41 (35%)</td>
</tr>
<tr>
<td>Recurrent infarction deaths</td>
<td>13 (11%)</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Total patients with recurrent infarction</td>
<td>28 (24%)</td>
<td>43 (36%)</td>
</tr>
</tbody>
</table>

Table 3.—Bjerkelund’s Trial.\textsuperscript{185} Deaths and Recurrent Infarction in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulant Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with</td>
<td>Men (88 patients)</td>
<td>Men (93 patients)</td>
</tr>
<tr>
<td>Recurrent Infarction</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Deaths</td>
<td>Women (31 patients)</td>
<td>Women (25 patients)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4.—M.R.C. Trial. Deaths in Males and Females

<table>
<thead>
<tr>
<th>Period Since Admission in Months</th>
<th>Low Dosage (188 patients)</th>
<th>High Dosage (195 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 6</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>6-12</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>12-24+</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>22</td>
</tr>
</tbody>
</table>

The Medical Research Council trial\textsuperscript{187} differed from Bjerkelund’s principally in three ways: (1) one group of patients received sufficient phenindione to prolong their prothrombin times by the one-stage technic to 2-2\textfrac{1}{2} times the control clotting time value (high-dosage group), and the other comparable group received identical appearing tablets containing only 1 mg. of phenindione (low-dosage group) which did not prolong the prothrombin time; (2) patients were randomly allocated to the 2 treatment groups at each participating center; (3) treatment was identical for the 2 groups including venipunctures at 1- to 3-week intervals. The trial was not double-blind in that the clinicians directing the program knew the treatment group to which each patient belonged. The overall mortality was clearly reduced in the high dosage treated males only during the first 6 months of treatment (tables 4 and 5), while reinfarction was less throughout the entire trial (table 6). High-dosage treatment primarily protected males under 55. Compared with the low-dosage group the death rate was reduced to one-half in high dosage males under 55 and to two-thirds in the group age 55 and over; reinfarction was reduced to one-fifth in these younger males and to one-half in the older males. The differences in reinfarction are statistically significant while the differences in mortality are not.

Clausen and associates\textsuperscript{188} studied 192 patients randomly divided into
treated and control groups. They found the incidence of recurrent infarction in treated patients under age 55 to be significantly reduced during the first year of treatment. This benefit did not continue into the second year, nor were patients 55 years of age or over similarly benefited. Mortality was not significantly altered by anticoagulant therapy.

The results of the trials of Bjerkelund, the Medical Research Council and Clausen are quite similar. All show anticoagulant therapy to reduce mortality and recurrent infarction primarily in younger men during the first 6 to 12 months of treatment. In other patients anticoagulant therapy was much less beneficial.

Harvald, Hilden and Lund conducted a well designed controlled clinical trial in which patients were allocated into comparable treated and control groups according to date of birth. The anticoagulant group receivedbishydroxycoumarin or phenprocoumon and the control group received placebo tablets. Venipunctures were performed with similar frequency in both groups. There were a total of 315 patients, 145 treated with anticoagulants and 170 treated with placebo. During the first year of the trial there seemed to be a lower incidence of reinfarction and mortality in the treated group, but the difference was significant ($p < 0.05$) only with regard to the reinfarction
rate in patients age 60 and over (table 7). Whatever prophylactic effect was
present during the first year had disappeared by 2 years since after that
time there were no significant differences between the 2 groups regarding
recurrent infarction or mortality (table 8). Despite the fact that the overall
mortality was not appreciably influenced there were significantly (p <
0.05) fewer thromboembolic complications in the anticoagulant group (10
in the anticoagulant group against 28 in the placebo group).

The authors concede that anticoagulant therapy might exert a “certain
prophylactic effect,” but since in their experience the effect of such therapy
on mortality was only slight at best, they do not consider it justifiable to rec-
ommend anticoagulant therapy routinely after myocardial infarction.

The early results of Aspenström’s double-blind controlled clinical trial190
revealed somewhat different results. He found that males age 60 and over
receiving anticoagulants had significantly fewer recurrent infarctions
and death during the second to fourth years of observation than a com-
parable group receiving placebo therapy (tables 9 and 10). Women under
age 60 also had strikingly fewer recurrent infarctions when treated with
anticoagulants, but this finding is based on a total of only 13 patients.

During the first year of anticoagulant therapy men age 60 and over were
protected from recurrent infarction but not from death (anticoagulant
group: 1 recurrent infarction, 9 deaths; control group: 5 recurrent infar-
ctions, 6 deaths).

Using the criteria of Russek and co-workers191 for dividing the patients
into “good risk and poor risk” groups at the conclusion of the first hospitaliza-
tion, Aspenström found that although anticoagulant therapy benefited both
groups to some extent the major protection seemed to be in preventing recur-
rent infarction in the “poor risk” group (table 11).

In 1963 the results of this trial showed the same tendency as in 1960:192
“those with the most unfavorable prognosis because of a permanently in-
creased risk of thromboembolism will benefit the most from anticoagulants.”

In 1963 there were 118 patients treated with Dicumarol, 78 of whom were
“poor risk” patients, and 113 treated with placebo, 80 of whom were in the
“poor risk” category. Among the “good risk” patients the incidence of in-
farction and thromboembolic episodes, as well as the 5 year mortality of
“about 10 per cent,” were essentially the same in the anticoagulant and con-

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Table 9.—Aspenström’s Trial. Influence of Age on Mortality and Recurrent Infarction

<table>
<thead>
<tr>
<th></th>
<th>Observation Mo.</th>
<th>Deaths</th>
<th>Recurrent Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males &lt; 60</td>
<td>25</td>
<td>696</td>
<td>4</td>
</tr>
<tr>
<td>Males ≥ 60</td>
<td>35</td>
<td>859</td>
<td>10</td>
</tr>
<tr>
<td>Females &lt; 60</td>
<td>7</td>
<td>251</td>
<td>1</td>
</tr>
<tr>
<td>Females ≥ 60</td>
<td>21</td>
<td>606</td>
<td>5</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>88</td>
<td>2,412</td>
<td>20</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males &lt; 60</td>
<td>24</td>
<td>749</td>
<td>5</td>
</tr>
<tr>
<td>Males ≥ 60</td>
<td>36</td>
<td>907</td>
<td>16</td>
</tr>
<tr>
<td>Females &lt; 60</td>
<td>6</td>
<td>177</td>
<td>2</td>
</tr>
<tr>
<td>Females ≥ 60</td>
<td>25</td>
<td>608</td>
<td>11</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>91</td>
<td>2,441</td>
<td>34</td>
</tr>
</tbody>
</table>

*p ≤ 0.01.

Table 10.—Aspenström’s Trial. Deaths and Reinfarction in First and Subsequent Years

<table>
<thead>
<tr>
<th></th>
<th>Observation Mo.</th>
<th>Deaths</th>
<th>Recurrent Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &lt; 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st year</td>
<td>269</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2nd–4th year</td>
<td>427</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Men ≥ 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st year</td>
<td>345</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>2nd–4th year</td>
<td>513</td>
<td>1†</td>
<td>0*</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &lt; 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st year</td>
<td>269</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2nd–4th year</td>
<td>480</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Men ≥ 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st year</td>
<td>392</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>2nd–4th year</td>
<td>514</td>
<td>10†</td>
<td>5*</td>
</tr>
</tbody>
</table>

*p ≤ 0.05.
†p ≤ 0.001.

Seaman and associates\textsuperscript{65,194} have been conducting a controlled double-blind study for 7 years. Their preliminary results based on only 196 patients randomly allocated into 3 groups—anticoagulant, placebo, and control (receiving neither anticoagulant nor placebo)—have, so far, failed to show benefit from anticoagulant therapy. Lovell and his group\textsuperscript{105} also have a continuing long-term study involving about 250 patients. Their results also permit no conclusion to be drawn at this time.
Many other long-term studies have been completed\textsuperscript{57} but the comparability of the control and treated groups and the method of allocation into these groups has been less satisfactory. The results of these trials, though generally favoring long-term anticoagulant therapy after myocardial infarction, must be considered less acceptable.

Since 1960 we have been conducting a controlled double-blind study which fulfills the rigid criteria demanded by Douglas.\textsuperscript{57} This study is incomplete and the numbers of subjects too small for firm conclusions. To date it appears that females receive some benefit from anticoagulant therapy during the acute phase after myocardial infarction but not from long-term therapy. Males as yet have not benefited either in the acute or long-term phase. We have stopped anticoagulant therapy abruptly either at the end of the hospitalization period or after 1 year in over 100 patients without observing any increase in deaths or recurrent infarction during the subsequent weeks. We have not been able to substantiate the existence of a “rebound phenomenon.”\textsuperscript{48,196,197}

Conclusion: The question of long-term anticoagulant therapy after acute myocardial infarction is still relatively unresolved. Women have not been shown to benefit except in one published trial\textsuperscript{190} where only 13 patients were involved. Men seem to benefit but the controlled trials reported to date disagree as to which groups of men should be treated and for how long therapy should be continued (table 12). Thus this therapy is of limited value, and a particular group which may benefit is likely to be obscured by the extensive dissimilarities of the subjects composing clinical trials. Certainly long-term anticoagulant therapy does not fulfill the therapeutic needs of patients who survive acute myocardial infarction, but since a more satisfactory form of treatment is not yet available it should be utilized pending further information, especially since if properly used it is not likely to be harmful. This means that men surviving acute myocardial infarction who have no contraindications to anticoagulant drugs should be treated. The duration of therapy would depend primarily on the ability of the patient to participate satisfactorily, the facilities available and the availability and enthusiasm of the physicians involved rather than on definitive proof of efficacy.

**Final Discussion and Conclusions**

Theoretically anticoagulant therapy is of most value in situations where the vascular pressure is low and stasis tends to occur. In effect this means the venous circulation and the left atrium. Clinically this is borne out by the unmistakable benefits of anticoagulant therapy in patients with deep vein throm-
Table 12.—Long-Term Anticoagulant Therapy

<table>
<thead>
<tr>
<th></th>
<th>Older Men</th>
<th>Younger Men</th>
<th>Within 1st Year</th>
<th>Beyond 1st Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjerkelund</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.R.C.</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clausen et al.</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvald et al.</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspenström and</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bengtsen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of major benefits (+) in men observed in controlled trials (areas not marked indicate lesser benefit or no benefit).

bosis, pulmonary embolism, atrial fibrillation with mitral stenosis, and during prolonged bed rest.

The value of anticoagulant therapy in the arterial circulation is more debatable. Short-term therapy appears to be beneficial after acute myocardial infarction perhaps largely by the prevention of pulmonary embolism. It may also be of value in impending myocardial infarction but additional trials are necessary.

Long-term anticoagulant therapy provides a limited degree of protection after myocardial infarction in men. Men with early angina pectoris may also benefit but too few trials have been completed.

In cerebrovascular disease anticoagulant therapy does not seem to be of value in completed strokes; it may even be harmful. Transient ischemic attacks are reduced in number with long-term therapy, but an appreciable influence on mortality has not been unequivocally demonstrated.

On the basis of the existing though inadequate evidence we currently suggest its use in appropriate patients with the following conditions: (1) deep vein thrombosis, pulmonary embolism and conditions predisposing thereto; (2) peripheral embolism emanating from the heart, especially the left atrium; (3) transient cerebral ischemic episodes; (4) after myocardial infarction during the acute phase in both sexes and during the long-term phase in men.

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