ANTICOAGULANT THERAPY

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I. INTRODUCTION

The clinical success of anticoagulant treatment must be one of the great illogical triumphs of modern therapeutics. This statement will seem surprising

to those who are unfamiliar with the fundamental difference between thrombosis and clotting; since these two terms are still widely treated as synonyms, a brief explanation will be in order at the outset.

It has been appreciated for many years that the initial and characteristic phenomenon of *thrombosis* is the deposition of platelets at a point on the inner wall of a blood vessel through which blood is flowing; this has been made clear from observations on intact vessels (50, 84b) as well as from experiments in various artificial circulations (8, 15, 162a, 192) and from histological examination (75). Other blood cells, as well as fibrin, accumulate to varying degrees as the thrombus extends, but these are secondary effects: platelet deposition is the fundamental occurrence. *Clotting*, on the other hand, has come to signify the conversion of fibrinogen to fibrin, and usually implies the solidification *en masse* of a given volume of stationary blood, whether *in vivo* as a static column in an occluded vessel, or in the cadaver, or *in vitro*.

The course of events initiating clinical thrombosis is still obscure. *Venous thrombosis* may apparently begin at several independent sites almost at once (187), without demonstrable evidence of local injury or abnormality: the evidence points to stasis, turbulence, or both as the localising as well as the precipitating factors in man (8, 187). Nevertheless it is often supposed that the localisation of the initial platelet deposit must be determined by some vascular lesion, however small, at that point. For this view there is some experimental evidence (15, 180, 181, 192, review in 245), and it may be demonstrable in *arterial thrombosis*, which is usually confined to diseased arteries and which shows certain differences from its venous counterpart (119a, 139a). It has been suggested that arterial thrombosis is initiated by tissue "thromboplastic" substances seeping into the arterial lumen from arteriosclerotic plaques and the like, and clotting the overlying blood. This hypothesis seems unlikely because in the condition known as the "defibrination syndrome," in which it is probable that tissue material is released into the circulation, fibrin forms as free strands in the circulating blood (131, 186). This presumably means that the coagulant substance is washed away from the point of its release before the clot forms, but perhaps a thin layer of blood is trapped in some way over an arterial lesion, so that this argument does not apply to thrombosis in atherosclerotic arteries. If clotting by tissue substances were an important factor in arterial thrombosis, one might expect the process to be sensitive to inhibition by the coumarin-indanedione drugs (Table 1) which specifically depress those plasma components required to activate the tissue material. Yet the clinical evidence is against this. Also, coagulant substances appear to be associated with muscle in vascular walls (84a); furthermore, muscular atrophy is characteristically associated with atherosclerotic plaques in coronary arteries (139a, p. 64), where the intima is often much thickened, so that material derived from the muscularis would not seem to be readily available at these sites. The hypothesis may be true, but at present it can hardly be supported.

The initial observations on heparin and dicoumarol showed that these agents interfered with blood coagulation, and indeed could be responsible for haemor-

TABLE 1

Names of anticoagulants

A large number of anticoagulant drugs has now been marketed, and their nomenclature has become progressively more involved. The following table is exhaustive neither in its list of drugs nor in the names given for the drugs which have been included, but is merely intended to cover the literature cited.

The name to the left-hand side is official either in the *BP* or *USP* or else is widely used as a generic name. As far as it has been possible to identify them, proprietary names have been capitalized; the same name appearing with a small letter indicates that it appears also to have been used in a generic sense.

The name employed in the text is generally that by which the reviewer believes the drug will be most widely recognized, and is *italicized* below.

1. COUMARINS	
acenocoumarol	acenocoumarin, G(eigy)23 350, Sinthrom, Sintrom 3-(α-acetonyl-*p*-nitrobenzyl)-4-hydroxycoumarin
bishydroxycoumarin	dicoumarin, dicoumarine, Dicoumarol, *dicoumarol*, Dicumarol, dicumarol, dicumarin, Melitoxin 3,3′-methylenebis(4-hydroxycoumarin)
cyclocoumarol	Coumopyrin, Cumopyran, cyclocumarol, Methopyranorin, Methanopyranorin 3,4-(2′-methyl-2′-methoxy-4′-phenyl) dihydropyranocoumarin
ethylbiscoumacetate	Pelentan, Tromexan, Tromexan ethyl acetate, *tromexan* 3,3′-carboxymethylenebis-(4-hydroxycoumarin) ethyl acetate
nicoumalone	Sinthrome 3-(2-acetyl-1-*p*-nitrophenylethyl)-4-hydroxycoumarin
phenprocoumon	Liquamar, Marcoumar, Marcumar, *marcumar* 3-(1′-phenylpropyl)-4-hydroxycoumarin
warfarin	Athrombin, Coumadin, Marevan, Panwarfin, Prothromadin, Warcoumin 3(α-acetonylbenzyl)-4-hydroxycoumarin
2. INDANEDIONES	
anisindione	Miradon, Maradone, anisindanedione 2-(methoxyphenyl)-1,3-indanedione
diphenadione	Dipaxin, dipaxin, diphenylacetylindanedione 2-diphenylacetyl-1,3-indanedione
phenindione	Danilone, Dindevan, Eridione, Hedulin, Indema, Indon, phenyl indanedione, "P.I.D." 2-phenyl-1,3-indanedione
3. *HEPARIN* PREPARATIONS	Depo-heparin Sodium, Hepathrom, Lipo-hepin, Liquaemin, Panheprin

Note: Structural formulae for a number of coumarin-indanedione drugs and Vitamin K analogues are given in Hunter, R. B. and Shepherd, D. M.: Chemistry of coumarin anticoagulant drugs. Brit. Med. Bull. **11**: 56–61, 1955.

rhagic disease (101, 102): the brilliant, but strictly speaking illogical, step was to apply them to the treatment of human thrombosis (22, 35, 42, 142). It is helpful to appreciate that in addition to side-actions three effects of anticoagulant drugs may be distinguished in clinical medicine: 1) they retard the clotting of blood; 2) in critical dosage they appear to be beneficial in at least some cases of thrombotic disease; and 3) in high dosage they lead to pathological bleeding. However, despite impressions to the contrary, we do not understand how these effects are related. Evidence is presented below that anticoagulants will reduce the adhesiveness of platelets *in vitro*, and will interfere with the haemostatic contribution of platelets in experimental wounds; however, we do not know that the same mechanisms operate in the initiation of thrombosis. Much work (*e.g.*, 26, 99, 238, 239, 249) has been done on the production of experimental vascular occlusion and the effects of anticoagulants thereon, but the occlusions have often differed greatly from natural thrombi (being obtained by such diverse methods as the injection of sclerosants, coagulants, microorganisms, serum, or serum extracts, or by heating, crushing, piercing, or corroding the vessel wall, or by two or more of these procedures together), so that the relevance of this work to clinical medicine is not always clear. The medical use of anticoagulants is still therefore essentially empirical; and the degree to which they will interfere with certain clotting tests in a given dosage is correlated only approximately with therapeutic benefit on the one hand, and haemorrhagic complications on the other. Clinical judgement is required if they are to be used to their full advantage. For this reason the reviewer has felt justified in allowing his own interests as a clinical pathologist to place the emphasis of the present review on the clinical use of anticoagulants and on the laboratory control of their dosage.

Mode of action. Considerable insight has been obtained into the nature of the interference with blood coagulation induced by various anticoagulants (9, 17, 45, 47, 54, 58, 72, 80, 81, 86, 91, 109, 115, 120, 125, 146, 170, 191, 197). Heparin has a direct anticoagulant effect on the blood itself, over the whole clotting sequence, in that it interferes immediately with coagulation when it is added to blood *in vivo* or *in vitro*. In contrast, the coumarin-indanedione group exert their effect only after ingestion, by interfering with the synthesis in the body (or perhaps liberation into the blood) of particular clotting factors. However, since we do not understand just how interference with clotting bears on either the therapeutic or haemorrhagic effects of these drugs, a detailed knowledge of this work is not required for their clinical use, and will here be passed over. Nevertheless, it is worth dealing briefly with the confusion, which is still sometimes troublesome, in the semantics of the anticoagulant activity of the coumarin-indanedione drugs. These agents have traditionally been called "antiprothrombic," whereas it is now realised that their ingestion leads to a fall in the activity in the blood of factors VII (proconvertin), IX (Christmas factor, plasma thromboplastin component, antihaemophilia factor—B or $-\beta$), and X (Stuart-Prower factor) as well as of prothrombin. The source of this confusion is historical. It happens that the anticoagulant effect of these drugs is more readily demonstrated when blood coagulation is initiated by the addition of tissue extract than when the blood is

simply allowed to clot on standing in a glass tube. This technique, now sometimes called the "accelerated clotting time," because the sequence of reactions involved leads more rapidly to the appearance of fibrin, was originated by A. J. Quick and associates in 1935 (168), before the introduction of anticoagulants. On the basis of the theory of blood clotting accepted at that time, the results of the test were logically interpreted in terms of prothrombin alone, as the originator has since described (165); the test was thought to measure the concentration of prothrombin in the blood, and became known as the "prothrombin time test." The technique became firmly entrenched in the anticoagulant field from the outset, when Link and his associates made it the basis of their biological work on the haemorrhagic agent finally identified as dicoumarol (36). The test has naturally passed over into clinical pathology to become the standard method for controlling the dose of the coumarin-indanedione drugs (19), retaining its misleading name despite experimental advances which have shown that the original test was relatively insensitive to prothrombin *sensu stricto* (18) (*pace* its originator, 166) but principally reflected changes in the activity of factor VII (to which we should now add factor X) (20 [figs. 35, 36], 78, 109). To make the method a more reliable index of changes in prothrombin and factor VII (and, in fact, X) Owren introduced (155) the modification known as the "P & P" method ("prothrombin and proconvertin"), and he has lately (150) further developed the test so that it should also be sensitive to changes in factor IX. The use of these and other tests will be discussed below. In any event, to report the result of a prothrombin time test as "% prothrombin" is misleading; this matter will be discussed more fully in a later section.

Of greater theoretical interest in thrombosis is the effect of anticoagulants on the platelets, but comparatively little has been done to elucidate the mechanism involved. Heparin acts directly to interfere with the cohesiveness of platelets to each other (175) and their adhesiveness to glass (245) (although apparently heparin may modify the glass as well as the platelets (32)), and reduces their coherence to the edges of experimental wounds (84b); the ability of heparin to prolong the bleeding time (31a, 175) may be mediated in this manner. Intravenous injections of commercial heparin have been found to produce transitory clumping of platelets and thrombocytopenia in the dog, but not in man or the rabbit (167). With dicoumarol, in both rabbits (246) and man (203) a reduction in platelet adhesiveness was noted after the drug was ingested for some days, without change in the platelet count in the circulating blood; in man (203) the degrees of change in the prothrombin time and in platelet adhesiveness were said to be broadly correlated.

There is evidence that anticoagulants increase the permeability of capillaries (242), but in treated patients the capillary fragility test has not shown a correlation between the readiness with which purpura can be produced and the occurrence of spontaneous bleeding (103, 162). Nevertheless, this would seem to be an important aspect for further investigation (16).

Other actions of anticoagulants may be mentioned briefly.

Heparin has a number of interesting activities. An injection during the period

of lipaemia following a fatty meal leads to a rapid clearing of the plasma (76); a lipolytic system is believed to be developed (172, 193), with a fall in plasma surface tension (6) but no change in plasma viscosity (233). This effect depends on the passage of heparin through the animal body, and many tissues will produce it (6, 236, 237); it is less marked in platelet-rich plasma than in platelet-poor plasma and is inhibited by a platelet extract (138); the quantity of heparin required is less than will delay clotting in whole blood but shows anticoagulant activity in platelet-free plasma (79); *in vitro*, the effect is small but has been found to involve Ca^{++} (66, 208). The fat-clearing system can also be activated by dextran sulphate (33, 97) and by polyethylene sulphonate (49). The physiological role of this system is still obscure; but it is interesting that in ischaemic heart disease the post-prandial lipaemia rises to higher levels than in control subjects, perhaps through differences in absorption (139), and that a given injection of heparin (300 u.) produced markedly less clearing than in the controls (147). The relation of heparin to the fat-clearing system has recently been reviewed in this journal by Robinson and French (172a).

After two to three days' administration, heparin is diuretic, both in normal subjects and in oedematous patients; heparin, thrombocid [xylan-polysulphuric acid], and Rol-8307 [N-formyl-chitosan polysulphuric acid] produce an excretion pattern which is similar to that seen in Addison's disease or after the administration of amphenone [1,2-bis(*p*-aminophenyl)-2-methyl-1-propanone·HCl] and the spirolactones, with Na^+-loss and slight K^+-retention (183). Heparin and Rol-8307 reduced the urinary aldosterone to normal levels in the face of salt restriction, thereby increasing the Na^+-loss; there was a synergistic effect with spirolactone (38). In dogs, an acute K^+-loss has been observed, unrelated to changes in aldosterone secretion (141); this was not seen in man (184).

Heparin interferes with mechanical activation of the frog egg (*Rana pipiens*) and other types of cell proliferation (77). Heparin applied locally has been claimed to be beneficial in the treatment of thermal injury (207), but the experimental evidence in man (111) and animals (5, 52) is conflicting. In the dog, injections of heparin prevented the eosinopenia and lymphopenia which ordinarily followed the injection of ACTH, cortisone, adrenaline, or insulin (67). In acquired haemolytic anaemia, heparin inhibited the reaction *in vitro* between the patient's red cells and the autoagglutinin (176), and on administration to the patient, saline agglutination of red cells and the Coombs' titre of the antibody were both reduced, with subsequent reduction of haemolysis *in vivo* (177); heparin also interferes with reactions involving complement, such as the Wassermann reaction; it also antagonises fibrinolysin (64). In the cold, heparin precipitates a fibrinogen-like protein from the plasma (110, 198, 199, 212), principally in inflammatory states; it is thought that this may be usefully related to other general tests for inflammation. The non-clotting actions of heparin were reviewed by Benditt (14a).

The coumarin-indanedione anticoagulants have been found to inhibit proliferation of fibroblasts in tissue culture (185) and, in rabbits, to hasten recanalisation in arteries occluded by injection of thrombin and morrhuate (247, 249);

in the latter case, the action of the anticoagulants was augmented by ACTH (247). Also in rabbits, treatment with phenindione increased the aortic cholesterosis induced by feeding cholesterol (133). Tromexan (34) was found to have a uricosuric action similar to that of probenecid (200); the observation that this drug inhibited the sickling phenomenon in a patient with the sickle-cell trait (73) could not be repeated (222). Tromexan has been claimed to be of value in deep X-ray treatment, reducing irradiation sickness as well as post-irradiation fibrosis of the treated region (44). A number of coumarin-indanedione derivatives has shown *in vitro* antibacterial activity (69); but in rabbits, dicoumarol treatment encouraged the spread of experimental streptococcal infection (214).

II. INDICATIONS FOR ANTICOAGULANT THERAPY

In this section of the review it is proposed to consider the evidence for the value of anticoagulant therapy in certain thrombotic disorders, particularly choosing those in which, on the one hand, a variety of opinions has been expressed and, on the other, good clinical investigations have been carried out.

As has been pointed out above, animal work has contributed little of immediate application to the basic clinical problem of when to use anticoagulants. Decisions must be based on the established evidence of benefits occurring in different types of thrombosis and on factors likely to affect the individual patient. While abnormal bleeding clearly shows that anticoagulants have done harm, it is far more difficult to know that the treatment has done good; for it is impossible to determine whether the individual patient would have been subject to further attacks or would have recovered more slowly from the initial illness had anticoagulants not been given. The evidence must therefore be largely statistical; this demands the comparison of attack rates, severity of illness, and mortality between comparable groups of treated and untreated patients. It is obviously very much more difficult to ensure comparability between clinical groups than between batches of biological material susceptible to laboratory manipulation. Nevertheless, the attempt must be made, and the evidence will be considered for various types of thrombotic disease. Problems such as administration will be considered later in this review; the present section deals simply with the primary question of whether, and when, anticoagulants may do good.

A. Cardiac infarction

It is a commonplace of controlled trials of drugs that the longer the subjects have to remain in the trial, the more difficult it is to ensure that the test and control groups remain comparable. For this there are two chief reasons. There are, first, the spontaneous variations in the natural history of the disease, which are especially important in an illness of such capricious morbidity and fatality as cardiac infarction. The illness may be mild or severe, and may change in severity during its course. Death may be immediate and sudden, or delayed for weeks, months, or years; death may be due directly to the initial infarction of the cardiac muscle, directly to a second or subsequent attack following the first after any interval of time, or indirectly to cardiac failure or emboli from intracardiac

thrombosis. Alternatively, during the period of acute illness, remote thrombosis may occur, for instance in the leg veins, which may cause death from pulmonary embolism. The other reason follows from the process of the trial itself; if the treatment has any effect on mortality, as time goes on the treated group will come to contain more and more persons whose counterparts in the control group have died. The varied natural history of the disease complicates greatly the matching of patients in test and control groups, and because of the effects of treatment, it is obviously easier to assess its benefit in the acute phase (*i.e.*, in the first three to four weeks after an infarct has occurred), while the patient is under continuous observation in bed, than in the subsequent months or years. These two periods will therefore be considered separately.

1. During the acute phase. The acute phase of myocardial infarction was one of the earliest disorders to which dicoumarol treatment was applied (35, 112); it was appreciated that while anticoagulants obviously could not reduce the immediate mortality due to massive infarction, they should certainly lessen the incidence of secondary thrombo-embolism (157). Important early evidence was obtained by the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction appointed by the American Heart Association, who arranged that patients admitted to several hospitals would be treated conventionally if presenting themselves on even dates, and would also receive dicoumarol for 30 days (with initial heparin optional) if presenting themselves on odd dates. There was inevitably considerable variation in the promptitude with which patients were referred to hospitals, and some had already received anticoagulants before admission; but in the analysis (252) of the first 800 cases (432 on anticoagulants, 368 controls) it was found that differences of age, sex, previous history of infarction, severity of illness present on admission, and institution of anticoagulant treatment before entering the trial were all reasonably well distributed between the two groups. There was a significant difference in the mortality rate in the first six weeks (controls 24%; treated 15%; $P < 0.01$), which was most obvious in the third and fourth weeks. The incidence of thrombo-embolic complication was likewise reduced in the treated group (controls 36%; treated 14%; but the latter value is reduced to 7% when the incidents are omitted which occurred during the first three days of treatment, *i.e.*, before anticoagulation would have been properly established, and also after dicoumarol had been withdrawn). Other studies confirmed these findings, including the first controlled series reported from Britain (221). However, the point has been strongly argued (179) that it is possible to divide cases of cardiac infarction into the categories of "good-risk" and "bad-risk," that the good-risk patients will have a low mortality anyway and should not be submitted to the inconvenience and hazard, even if small, of anticoagulant treatment, and that anticoagulants should be reserved for bad-risk cases where their benefit is the more apparent; nevertheless, the prognosis may not be clear when the patient is first seen (251).

An important criticism of the benefit of anticoagulants in the acute phase has been contributed by Honey and Truelove (83), who made a detailed analysis

of the experience of 543 patients admitted to the Radcliffe Infirmary, Oxford, over the period 1940 to 1954. Examining the effect of anticoagulants from 1952 to 1954, they concluded that the effect on mortality had been very small, and had affected only the incidence of pulmonary embolism. They pointed out that in an attempt to assess the benefit of anticoagulants from the experiences of control and treated series observed in parallel, it would be very difficult to exclude bias arising from unequal allocations of good- and bad-risk patients to the two groups for various good reasons strictly irrelevant to the conduct of the trial. They were even able to point to an earlier analysis based on the material which they were studying, in which it was possible to show that the favourable results adduced largely disappeared when bias in selection of cases had been allowed for; a similar criticism could be levelled at the final report of the American Heart Association's Committee. Other evidence of this order has been reviewed by McMichael (119).

Nevertheless, it appears that most authors have accepted the clinical value of anticoagulants in acute myocardial infarction, despite the real difficulties in the assessment of a hospital series extending over more than a short period of observation, and the even greater difficulties in comparing one series with another (51, 83, 118, 216). It is perhaps fair to say that the evidence for benefit from anticoagulants is not so good as would be demanded of an acute laboratory experiment (perhaps this is unattainable (31)); but that it would seem reasonable from all the data to expect that anticoagulants would at least reduce the danger of secondary thrombosis.

Recent synoptic views on the treatment of acute myocardial infarction, integrating anticoagulants with other measures, may be useful (65, 70), together with a theoretical discussion (132).

2. Long-term treatment. Obtaining valid evidence on the benefit of long-term anticoagulant treatment after coronary infarction has proved an unexpectedly stubborn problem, and it is important to appreciate clearly why this is so.

There have been two principal difficulties: the selection of appropriate criteria by which to measure the value of anticoagulation; and the determination of the expected course of the illness without treatment so that comparisons could be drawn.

Anent the first problem, it is helpful to distinguish, in the natural history of the disease, three classes of late sequelae, and to consider whether anticoagulants would be expected to influence them.

First, loss of contractile force through default of the infarcted muscle might impose on the remainder of the heart a strain comparable with the tax of valvular incompetence; if this leads to progressive cardiac failure, anticoagulants would not be expected to relieve it. Further, some degree of narrowing may have become established in various parts of the coronary tree by the time infarction occurs; from the consequent loss of arterial flow various symptoms may arise which again are unlikely to be reduced after the inception of anticoagulants, even should the treatment prevent a further reduction in arterial calibre. Lastly, pre-existent coronary artery disease may promote a subsequent occlusive thrombosis and

hence induce a recurrent myocardial infarction; and on this process anticoagulation might well be expected to impose a beneficent restraint. McMichael (119) argued that since coronary artery disease will tend to increase with age, this benefit should be most apparent in older patients. On the other hand, Gillam (65a) has suggested that in the elderly, a proportion of infarctions is instigated simply by atherosclerotic narrowing, whereas in younger hearts, where atherosclerosis is less, thrombosis is a relatively more important cause of infarction. He therefore suggested the likelihood of greater protection from anticoagulants in young, good-risk patients, where both the myocardium and coronary tree are relatively healthy.

Before being allowed to influence the course of argument, these speculations must be checked by clinical observation. The most nearly irrefutable clinical fact is death, and it is therefore natural to use a mortality rate as an index of the effect of treatment; but the above considerations show that upon only a proportion of cardiac deaths remotely following myocardial infarction would anticoagulation be expected to have an influence, so that mortality might not be a particularly sensitive measure to employ. Clearly the most specific index in a relapsing illness is the recurrence rate, but here there are particular difficulties in the diagnosis of recurrent infarction (119a, 244); some will be immediately fatal, and hard to distinguish from other causes of sudden death, while in others, the changes produced by the initial infarct will persist to obscure the findings, so that what is gained in specificity may be lost in disputability. Comparable difficulties arise with other indices which may be chosen.

The second problem hinges on the establishment of a comparable control group of patients with whose experience that of a treated group may be compared. Three types of comparisons have been used. The experience of individual patients under treatment has been contrasted with their own experience without treatment; this may be called "control-in-series." A treated and an untreated group have been observed side by side under similar conditions; this may be called "control-in-parallel." Thirdly, a more tenuous comparison may be drawn between a treated group and untreated material observed elsewhere or at another time; this may be termed "vicarious control."

Control-in-series eliminates systematic differences between patients, but in this instance has not been applied so as to eliminate the effects of the passage of time, since the treatment period has always *followed* the control period; treatment is thus applied during a later stage in the evolution both of the disease and of the observer's reactions to it.

Valid control-in-parallel depends on very accurately matching the patients in the treated and control series. In the first place, it has been found that the outlook after myocardial infarction will depend on age, sex, severity of the attack and degree of acute recovery, the presence of diabetes or of hypertension with enlargement of the heart or severe retinopathy, and perhaps on economic status (119a); the difficulties in matching two groups for so many characteristics will be obvious, but if this is not done, group comparisons cannot fairly be drawn. Again, the two groups must be supervised in precisely the same way throughout

the period of observation, or iatrogenic differences may be introduced; for instance, if the members of the control group are seen less frequently than the others, complications of rather insidious onset will go longer untreated, and may thus have a more adverse effect on the control population. Where it is known in which group a given patient has been placed, there are obvious reasons why those conducting a trial will not find it easy to make impartially the more difficult diagnoses (*e.g.*, recurrent infarct) if upon them will depend the immediate disposal of their patients as well as the ultimate results of the trial. This is not blameworthy, for it arises out of clinical responsibility, but the operation of this kind of bias must be faced, and indeed has been forcibly pointed out in connection with acute-phase trials (83). Furthermore, any selective benefit of the treatment which affects mortality will progressively undermine the comparability of the two groups as the trial progresses, so that it will become increasingly difficult to compare the remote experiences of the survivors. With so many conditions to observe, it is inevitable that the patients who can be collected for any given trial will tend to be few, so that unknown and random differences between the groups will be relatively important.

Vicarious control is advantageous if it allows larger numbers of patients to be studied; but the method is valid only if the variability within the control and treated groups can be assessed independently, so that the final comparison can be set up on the general lines of a test for the significance of the difference between two means. So far this has been achieved by accumulating a number of control and treated series from the literature, and by using the variability between like series as a measure of the error term.

The case for trying long-term anticoagulation in coronary disease was early apparent (56, 143), and by 1954, at the Basel Conference on Thrombosis and Embolism, several series could be reported (43, 57, 149); the speakers' results were encouraging but the ensuing discussion was cautious.

Since then, many favourable series have been published.

a. Control-in-series has been reported in the form of attack rates. For instance, I. S. Wright's group (55) observed 23 patients (who previously had had one or more coronary infarcts) for 628 patient-months before starting anticoagulants, and then for a further 847 patient-months on anticoagulant therapy. In the pretreatment period the rate of occurrence of thromboembolic episodes was *ca.* 10 per patient-month, whereas on treatment it fell to *ca.* 0.5 per patient-month.

b. Control-in-parallel has been the basis of several important trials. For instance, over a period of years Manchester (123) saw 404 patients in an acute attack of coronary infarction, and alternate persons were treated thereafter with anticoagulants with ascorbic acid (204 patients), or with ascorbic acid alone as the control group (200 patients); regular prothrombin times were done in both groups, and other treatment was comparable except that 23 of the control group had had anticoagulants in the acute attack and were then transferred, and that 66 patients in the control group were digitalised for cardiac failure as against 32 in the anticoagulant group. All these patients cooperated with the regimen and were observed up to the end of the ten-year intake period or until prior death,

so that individuals were under treatment or observation from one to ten years. Age-, sex- and initial severity-distributions were generally similar for the two groups, although more patients had had previous infarction in the anticoagulant group. During the period of observation, the incidence of subsequent infarction in the control group was 34%, with a mortality from all causes of 43%; in the anticoagulant group the figures were 14% and 8%, respectively. In terms of patient-years, the control group suffered 8 subsequent infarctions and 5 deaths per 100 years, whereas for the anticoagulant group the rates were 3 and 0.5, respectively. Benefit was apparent at least over the first four years from the initial infarct. By contrast, the incidence of angina was the same in the two groups, a point stressed by McMichael (118).

A similar method was used by Bjerkelund (25), in his very careful follow-up study of 237 cases who had been treated with anticoagulants for one month following an acute attack of coronary infarction, and were again so treated in any subsequent acute attacks; apart from this, 119 cases were kept on continuous anticoagulant therapy, and the remaining 118 cases served as the control group, the allocation depending on which hospital service the patients had entered with the initial attack (although they were all supervised by the author). Retrospective analysis confirmed a fair distribution of patients between the two groups, according to general characteristics, past history, and the severity and treatment of the initial acute episode. The control group did not receive a *placebo* or undergo regular venepuncture but were otherwise followed similarly, except that they were seen rather less frequently than the treated patients. The over-all incidence of recurrent infarction among the controls was 32% as against 19% in the treated group, but the difference was significant only in patients under 60 years of age and for the first year of continuous treatment. A similar result was obtained in the analysis of mortality; but here, over-all female mortality was apparently unaffected by treatment whereas male mortality was reduced about one-half in those treated. As in Manchester's series, no difference was observed in the incidence of angina pectoris between the two groups.

It appeared further that patients who had suffered only one infarct benefited more than those with several previous attacks, leading the author to suggest that it is the good-risk patient who gains most from long-term treatment. This is consonant with the reasonable idea that long-term anticoagulation is prophylactic rather than curative. On the other hand, Suzman *et al.* (207a) came to the opposite conclusion after studying 170 patients: namely, that those with a mild initial attack treated with anticoagulants in the acute phase did well whether or not the treatment was continued thereafter, whereas those with a history of previous episodes and a severe presenting attack were likely to benefit from long-term treatment. However, the treated and control groups were imperfectly matched with respect to evidence of previous coronary artery disease.

Ensor and Peters (53) compared a series of 408 patients maintained on anticoagulants, with 140 patients who started on anticoagulation but discontinued the treatment after varying lengths of time, and also with untreated series from the literature; at 5 years the mortality in the three groups was calculated to be

21%, 29%, and 42%, respectively, and at 10 years to be 25%, 36%, and 68%, respectively. Clearly the comparability of these three groups needs careful scrutiny, for on the one hand it is possible that the transfer of patients from the first to the second group (on cessation of treatment) might be associated with some characteristic which would affect mortality, and on the other hand many circumstances might have introduced differences between the prognosis of the authors' own patients and those cared for by others.

To guard against the uncertainties of such perturbations, the Working Party (243) on anticoagulant treatment set up by the Medical Research Council (reporting in 1959) employed a rigorous design for the selection and allocation of patients to control and treatment groups, and laid down clear criteria for the assessment of results. Divided among 15 hospital centres in Great Britain, 383 patients were accepted, of either sex, 40 to 69 years of age, between the 29th and the 43rd day after the onset of an acute infarction, and showing Q-wave evidence on the electrocardiogram (early anticoagulant treatment optional); they were classified according to their previous history of infarction (none, one, or more than one) and divided into two groups: the one (165 males, 30 females) received full anticoagulant treatment with phenindione, controlled in a standardised manner ("full dosage"), and the other (160 males, 28 females) received standard tablets containing 1 mg of phenindione ("token dosage"). The allocation, by a prepared code, ensured that at each centre patients of each category of previous infarction should be allocated at random to each dosage group, and at each centre all patients were otherwise comparably cared for. In addition, criteria were laid down for exclusion from the trial, such as the presence of various other serious illnesses, both non-cardiac and cardiac (including uncontrolled heart failure), the likelihood of haemorrhage or drug sensitivity, and pregnancy; for these reasons only about one-third of the available patients could be accepted for the trial. Treatment was temporarily interrupted if operations or dental extractions were required, and further infarctions occurring in either dosage group were treated *secundem artem* for up to 42 days; unless there then appeared one of the indications for exclusion from the trial, the patient was returned to the original group.

A retrospective analysis showed good comparability between the treatment groups with respect to age and sex, and previous history of angina, claudication, and diabetes. Withdrawals from the two dosage groups were equal in number and showed over-all a similar mortality; but whereas of the 23 patients withdrawn from the token-dosage group, 10 were removed following further thrombo-embolism and none on account of bleeding, 14 patients were withdrawn from the full-dosage group on account of bleeding or danger of bleeding, and only one because of thrombosis (a clinical diagnosis of cerebral thrombosis), out of 24 removed from this group for all causes. In assessing results, the experiences of all these patients were included only up to the time of withdrawal.

With this provision, 31 deaths occurred within the trial in the token-dosage group (28 ascribed to recurrent infarction) and 22 in the full-dosage group (18 ascribed to recurrent infarction, one to cerebral haemorrhage); female experience

was too small for analysis, and in fact the difference between the groups was determined by the male experience, which showed a rather clearer benefit from full treatment below the age of 55 years than above; but none of the differences in mortality between the treatment groups was significant (an intermediate analysis had shown a more promising benefit from treatment and limited the continuance of the trial (244)). However, when patients excluded from the trial on account of further infarction (9 on token dosage) or the development of cardiac failure (4 on token dosage, 3 on full dosage) were combined with the deaths, it was possible to show a significant effect of treatment among the younger males (for males at ages 40 to 54 years, 19/69 [19 out of a total of 69] deaths and exclusions in the token dosage group as compared with 8/73 on full dosage). With respect to the incidence of all subsequent infarction among males in the two groups, 33 occurred among the 69 token treatment males aged 40 to 54, as compared with 8 among the corresponding full-treatment males.

When the male experience was analysed by duration of treatment, the incidence of withdrawals was similar in the two groups. The advantage in mortality rate of the full-dosage group was confined to the first three-monthly period in the trial, but the protection from further infarction afforded by the higher dosage was apparent into the second year after the initial incident. An analysis of various symptoms and of return to work among male survivors remaining in the trial showed, on balance, little difference between the treatment groups; thus, on an average 71% of survivors returned to work on the lower level of treatment as against 83% on the higher level.

The Working Party indicated the concurrence of their findings with Manchester's of a prolonged reduction in (re)infarction rate, and their agreement with Bjerkelund that, on the other hand, the reduction in mortality is apparent only in the early months of treatment. They also pointed out that this must destroy the comparability of the two groups of patients at a fairly early stage in the trial, for the full-dosage group would continue to hold patients whose counterparts in the other group had died in the first few months. The general application of the findings is also limited by the intentional selection of patients for the trial, and this selection may also have heightened any bias introduced through the attending clinicians' knowing (as it was clear that they had to know (244)) into which treatment group their patients were placed; for it would have been difficult to avoid taking a special interest in the one-sixth of one's new coronary patients in one treatment group and another sixth in the other.

McMichael (119) criticised the Working Party's report on various counts. He pointed to the high lethality among the (fewer) recurrent infarcts in the treated group, and to the fact that a reduction in mortality was not seen among the older patients in whom atheromatous changes would be expected to be more severe, and who might therefore be expected to be at a greater risk of thrombosis. He also drew attention to various other reports in which the findings differed from those of the Working Party's trial. Honey and Truelove (84) felt that the addition of the patients withdrawn to the patients who died would bias the token-dosage group, because a physician, knowing his patient to be in this

group, would very readily withdraw him (that is, treat him on full anticoagulation) as soon as he presented signs of reinfarction (it is not clear from the report how these were defined), whereas patients in the full-treatment group would perhaps have been allowed to continue in the trial (*i.e.*, under adequate anticoagulation) until more severely ill.

In a reply (244), the Working Party explained their difficulties in defining reinfarction but gave the working arrangements which were adopted, which would perhaps not entirely have eliminated the risk to which Honey and Truelove drew attention, although reasons were given for thinking that the risk was not great.

The capriciousness of small numbers in studying so variable a disease as coronary infarction (119a) is well shown in a study conducted by MacMillan, Brown and Watt (121a) on lines similar to the Working Party's trial. Over the year 1958, patients accepted for the study were allocated at random to high or low doses of dicoumarol; prothrombin tests and supervision were the same in both groups. Among 23 high-dosage patients, recurrent infarction was diagnosed in six; in addition, there were eight deaths (five "sudden," and three others probably due to recurrent infarcts). On the other hand, among 27 low-dosage patients, the diagnosis of recurrent infarction was made in only four, and there were no deaths. These results emphasise that the numbers of patients included in such a trial must be sufficiently large for the incidence of morbidity and mortality in the control group to be significantly different from zero (in this case, note especially the death rate) before the experience of the treated group can usefully be compared with it. The possible advantage of vicarious control in allowing a far greater number of patients to be studied, must therefore be carefully considered.

c. Vicarious control. Owren (151) collected three untreated groups and two treated groups, whose mortalities seem respectively comparable (Fig. 1, reproduced from his paper). An ingenious feature of this comparison is that the two families of curves are linked by Bjerkelund's data (already discussed) which were derived from the experience of patients from a reasonably homogeneous environment (almost all living in Oslo). The figure shows a clear difference between the treated and the control patients. McMichael and Parry (119a) later collected a much larger number of series. They were able to plot the percentage survival for periods up to 10 years following first infarction in eight untreated series including in all 1784 patients; with one unusually favourable exception, the curves were closely grouped, and showed an average 5-year survival of about 65% (this material did not include the various control groups detailed by authors reporting the results of treatment). In 10 treated series, including *ca.* 2,000 patients (some of the patients may have been included in more than one of the series; also, one of the series included patients with angina), the corresponding average survival was about 75%. This straightforward comparison was confused by two features. First, the survival in none of the treated groups attained the 5-year figure of 83% observed in the one exceptional untreated group (123 doctors aged 40 to 64 years who had survived their acute infarction by more than

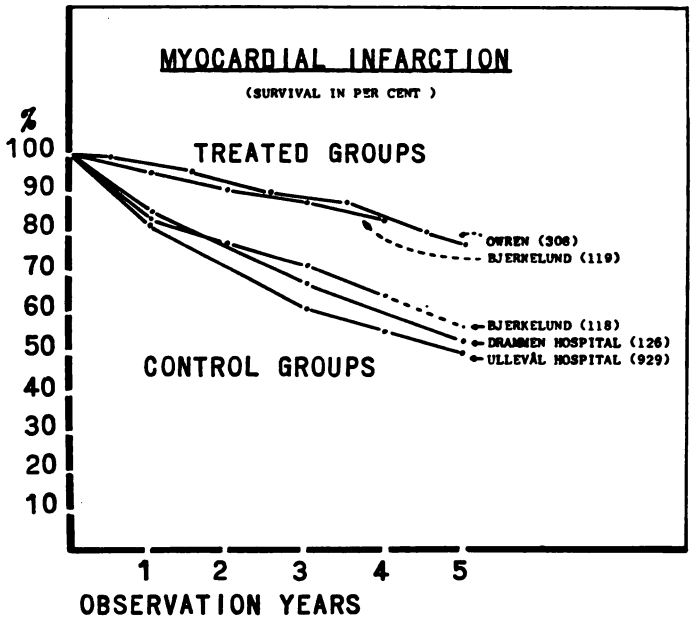

FIG. 1 [Owren (151), Fig. 3]

"The effect of lifelong anticoagulant therapy on mortality of survivors of acute myocardial infarction"

Owren pointed out that the average mortality is about 5% per year in the two treated groups and about 10% per year in the control groups. Note that this pooling of results tends to obscure the predominant effect of treatment in the first year in Bjerkelund's data alone. Numerals in parentheses on the figure indicate the number of patients in each group.

one month), and second, in three instances (one of which was Bjerkelund's (25)) the experience in the control groups reported along with treated material was worse (in one, conspicuously so) than in the untreated series referred to above. Two questions therefore remain. Would treatment have even bettered the 83% 5-year survival among the doctors? If not, this would raise the possibility that the improvement apparently associated with treatment in other series was due to some factor other than anticoagulants (such as frequent supervision). And, since the controls for three treated series appear to be unfavourably loaded, does this invalidate the inclusion of their corresponding treated material in the general comparisons laid out above? If so, the tentative conclusion of a beneficial effect of treatment becomes uncertain.

It may not be entirely fair to use the medical series on a par with the others. It is possible that this group includes a disproportionate number of presumptive diagnoses, on the basis that a cardiologist approached by a colleague complaining of suggestive symptoms would perhaps tend to make the diagnosis of cardiac infarction a little more readily than in other patients; since the data for this group were obtained from insurance records it might further be difficult for presumptive initial diagnoses to be revised at a later stage. Also, as Todd (215a)

suggested, the doctors' group might contain a number of mild cases which, in non-medical subjects, would have escaped diagnosis (the symptoms being regarded, for instance, as "indigestion"). This explanation is supported by the pattern of deaths in the group, which shows a very sharp fall in the death-rate after one month, as though the survivors at the second month were predominantly mild cases. In the three control series with especially high mortality, it is difficult to be sure that the patients are comparable to those in the original group of untreated series of cases with a single previous infarct. A study of the papers from which the three are derived suggests that there may have been differences in average age and that patients included may have had more than one previous infarct.

While some of McMichael and Parry's detailed criticisms of previous work may thus have been over-stringent, the importance of their paper must be fully acknowledged. Their appreciation of factors influencing prognosis is quite fundamental to the study of therapeutic benefit; and it will be of the greatest value if their work gives pause to the over-enthusiastic extension of a time-consuming treatment to many who will not benefit proportionally from it. Unless the large-scale administration of anticoagulants is constantly passed under critical review, it is likely, in the nature of the human situation, that the effort and organisation which long-term treatment demands will lead to a self-justifying and self-perpetuating system. Even on a favourable interpretation of the evidence one must conclude that the effect on mortality is likely to be rather small: *cf.* the average 5-year survivals of 65% and 75% in McMichael and Parry's groups of series. The situation is reminiscent of an analysis of variance with a small main effect and a large residual error, or of a "noisy" circuit with a scarcely audible signal. One would not work with either of these tools unless there was no alternative; but until there is a more efficient treatment for coronary infarction, we must try to define those patients to whom anticoagulants are likely to bring benefit, realising that in the attempt we shall undoubtedly treat many whose clinical course will not thereby be influenced at all.

B. Angina pectoris

The subjective nature of this symptom obviously makes it difficult to judge the degree of relief afforded by anticoagulants, and the varying natural course of the disease creates further problems (25). How much a patient will be troubled by angina will also be affected by the amount of activity which his other symptoms will permit, so that it will be hard to disentangle a specific treatment effect on angina from other benefits.

Neither Manchester (123) nor Bjerkelund (25) felt that angina had been clearly benefited, and the M.R.C. Working Party (243) detected only a small benefit from treatment.

On the other hand, Owren (151) examined the *mortality* of patients complaining of angina and stressed the importance of the interval between the onset of symptoms and the initiation of treatment; Figure 2(A and B) reproduces his comparisons derived from the studies of Waaler (229) and Block *et al.* (29). The

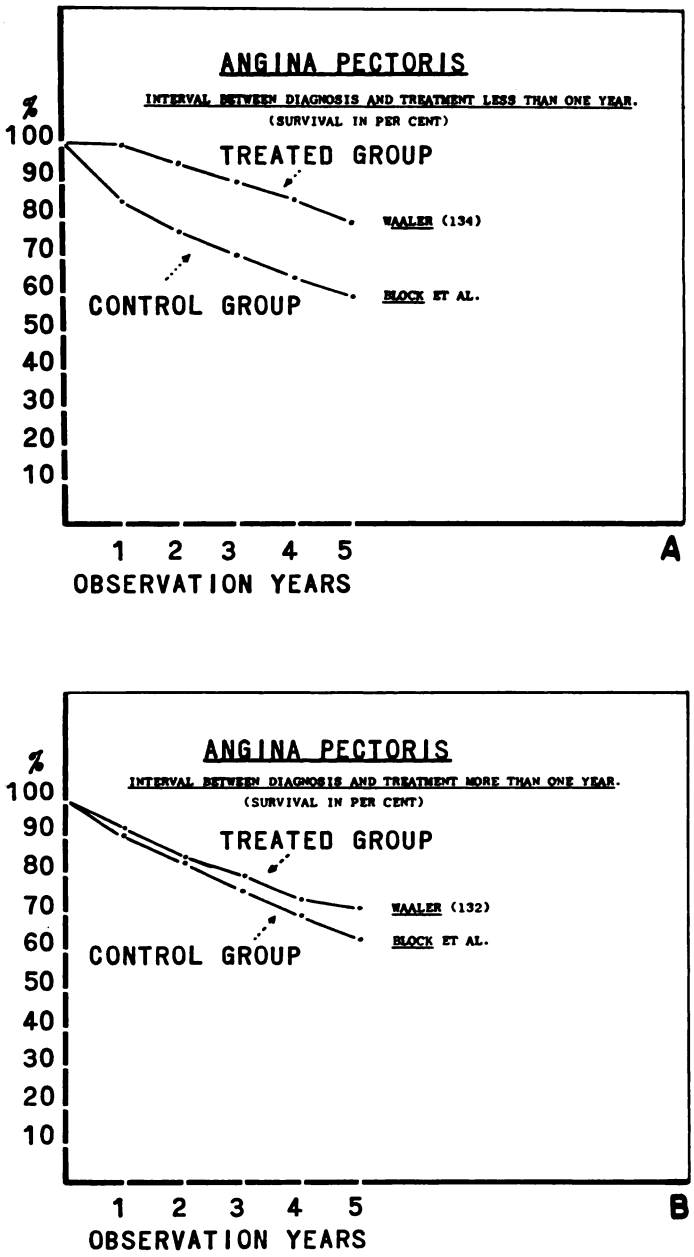

FIG. 2 [Owren (151), Figs. 7 and 8]

"Effects of anticoagulant therapy in angina pectoris with short (A) and with long (B) duration of symptoms prior to therapy"

The data are from Waaler (229) and Block *et al.* (29) (who studied 6,882 cases). Numerals in parentheses attached to Waaler's curves show the numbers of patients in the groups.

internal evidence of Figure 1 for the comparability of the material is wanting here; the comparability of environmental factors is also more doubtful. Nevertheless, two points are interesting: first, the close similarity of experience in Figure 2(B); second, in Figure 2(A) the curves run parallel after an initial divergence in the first year, a situation very similar to that seen in Bjerkelund's coronary infarct material. Owren's analysis therefore suggests that if angina pectoris is treated from the onset with anticoagulants, a certain number of early deaths will be prevented. Indeed, this may be another way of approaching the same phenomenon as Bjerkelund and the M.R.C. Working Party recorded.

At the time of completing this review, the most recent investigation was that of Borchgrevink (31), who studied 203 patients, 147 having angina pectoris only, of less than two years' duration (males 114, females 33), and 56 having suffered one coronary infarction three months or more previously (males 50, females 6). All were below 70 years of age, with a diastolic blood pressure of less than 95 mm Hg, and free from valvular disease, failure or enlargement of the heart, other disease which might cause death within the observation period, or contraindications to anticoagulation. Upon acceptance for the trial, each patient was classified by sex, history (angina only, or previous infarct), and serum cholesterol concentration (below or above 400 mg%). All were then treated continuously with phenindione (rare exceptions received dicoumarol), the drug having been allocated by random numbers at high or moderate dosage within each of the eight classes derived from the three above criteria (since it was thought no longer justifiable to maintain patients without anticoagulants or on only a token treatment). It was argued that a difference between the clinical course of the two treatment groups would indicate a greater benefit from higher dosage, and therefore by implication provide evidence that anticoagulation was in fact beneficial.

The high-dosage group (103 patients) each received an average of 110 mg phenindione daily, maintaining P & P values of 10 to 30%, whereas the moderate-dosage group (100 patients) received an average of 65 mg daily and maintained P & P values at 40 to 60%. Moderate-dosage patients developing infarction under treatment received high doses during the acute phase and were then returned to moderate dosage. Anticoagulation was controlled by Borchgrevink's laboratory and all patients were personally examined every six months, being meanwhile clinically supervised by their own physicians, who were unaware in which treatment group the patient had been placed, as were the clinicians who made a final symptomatic assessment of each patient. This trial was begun in mid-1957, and from early in 1959 the results were studied sequentially on the bases of infarctions and of deaths. By the turn of the year, when observations were concluded, the sequential tests indicated a likely preference for high dosage on the basis of deaths and a clear preference on the experience of deaths and infarctions together.

In the high-dosage group, observations covered 142 patient years. One fatal and one non-fatal infarct occurred, with no other deaths. The moderate-dosage group covered 129 patient years, during which time eight cases died (5 from myo-

cardial infarction, 1 from cardiac failure, and two suddenly, thought to be cardiovascular deaths) and there were six non-fatal infarcts. In all there were thus reckoned to have been two infarcts (both in males) under high dosage and 13 (12 males, 1 female) under moderate dosage. The differences in infarction rate (per patient year) between the two treatment groups were significant for all males and for males with angina only, but not for females. The final symptomatic assessment also indicated a greater subjective improvement in the high-dosage group. It was not found possible to distinguish the fatal cases as a "bad risk" group, and Borchgrevink therefore concluded that continuous anticoagulation should be considered from the outset in all cases of angina. This suggestion is supported by the evidence of Figure 2.

C. Rheumatic heart disease

So chronic an illness as established rheumatic heart disease lends itself well to a trial of anticoagulants by control-in-series. At the Basel Conference, I. S. Wright (250) reported on 31 patients who had been observed for an aggregate of 39 patient-years before anticoagulation and for 59 patient-years on treatment: in the pre-treatment period they suffered 3.5 thromboembolic episodes per patient-year, but only 0.2 episodes per patient-year while on anticoagulants. Owren (151) followed 17 patients on anticoagulants for the same length of time as they had been under observation before treatment: this elegant comparison is set out in Figure 3. Prior to anticoagulation, 29 thromboembolic episodes were observed (with an additional 9 recorded in the anamneses); on anticoagulants only one, or possibly two, episodes occurred.

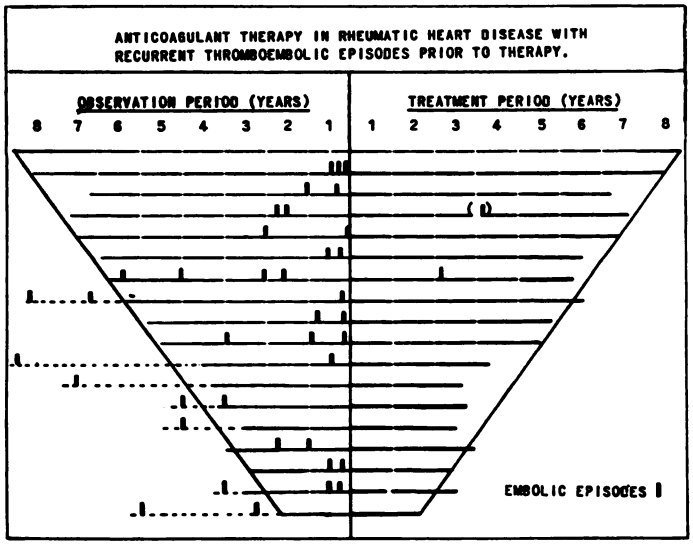

FIG. 3 [Owren (151), Fig. 1]

"The effectiveness of anticoagulant treatment in patients with mitral valvular disease and recurrent embolism prior to therapy"

Owren (151) also described a trial with control-in-parallel, recording the number of major embolic episodes after the first. Among 17 control patients there were 22 recurrent emboli in 81 patient-years, whereas 15 patients in the treatment group suffered no recurrent emboli in 60 patient-years.

Bannister (10) has recently discussed the advisability of early anticoagulation in patients with mitral stenosis. He pointed to the incidence of embolism among mildly affected patients (22 in his series of 105 patients from the Brompton Chest Hospital and the National Heart Hospital, London) before valvotomy was advised, and suggested that early anticoagulation might be tried as an alternative to earlier operation in many such cases.

D. Postoperative and recumbency thrombosis

1. In prevention. Much has been written on the value of anticoagulants in the prevention of postoperative and recumbency venous thrombosis (188); the Basel Conference received over a score of communications on this theme. Nevertheless there is still an evident lack of agreement on what ought to be done, and to whom prophylactic anticoagulants would be really beneficial; this dilemma is so important that its origins are worth briefly examining.

For instance, Barker and others (11) found 44% of 678 untreated surgical patients to develop postoperative thrombosis, with 18% (124 patients) dying from pulmonary embolism; whereas in 180 subsequently treated with dicoumarol, postoperative thrombosis occurred in 2 patients only, one of whom (0.6%) subsequently died of pulmonary embolism. On the other hand, Wise and others (241) found only 1.3% of "vascular complications" (including even transient signs) among 9,250 patients aged 20 to 80 years undergoing major abdominal surgery without anticoagulant treatment, as against 0.02% in 3,304 patients, contemporary with the last quarter of the control series, who received prophylactic anticoagulants.

While both these series point to the same general conclusion, their extreme quantitative differences would well excuse a certain bewilderment in persons reading such reports, and would hence condone the general attitude of *laisser faire* towards prophylactic anticoagulation which still confronts the enthusiasts. The evidence was made still more difficult to interpret because the introduction of anticoagulants was accompanied by a greatly increased clinical interest in thrombosis and its detection, so that diagnostic criteria may have been changing during the period through which series of patients were under study. Furthermore, other measures, such as early ambulation, were concurrently introduced in the hope of lowering the incidence of postoperative thrombosis. That this had a real effect is evidenced by the study of Hunter and others (87) who looked for *post-mortem* evidence of leg thrombosis in 169 patients who had been in the hospital more than two days, 39 of whom were known to have exercised or been ambulatory up to 48 hours before death, the remainder having been at rest in bed; in the first group thrombosis was found in 18% as compared with 53% in the second ($P < 0.01$). There is also the suspicion that the large early series were too heterogeneous to discern the relative value of anticoagulants for differ-

ent groups of patients; under present circumstances (and perhaps always) it is clearly unrealistic to envisage preventative anticoagulation for more than a proportion of those undergoing surgery or for any other reason confined to bed.

One of the difficulties of forming a judgement on this question stems from the nature of the evidence to be considered. There is no doubt that the obvious index of prophylactic value should be the mortality from pulmonary embolism, for not only is fatal embolism after operation an outstanding tragedy and deserving of all possible means of prevention, but it is a diagnosis which can be clearly established at autopsy. Yet fatal embolism is fortunately a relatively rare event, and so is difficult to study statistically; also, the individual surgeon will continue to be impressed by the large numbers of patients who do *not* suffer this complication. Further, the continuing occurrence of fatal embolism in a proportion of patients in whom there was not the least suspicion of venous thrombosis inevitably invests the tragedy with a certain aura of mystery so that it tends to be regarded as an "act of God" about which nothing could have been done.

This situation gives even more importance to the study of prophylactic anticoagulants in well-defined groups of patients. Two recent investigations deserve special mention.

Sevitt and Gallagher (188) studied 300 patients over 55 years of age, with either subcapital or pretrochanteric fracture of the femur, who were admitted under six different surgeons to the Birmingham Accident Hospital over a period of nineteen months. The series was derived from 319 consecutive cases available during the period; control-in-parallel was achieved by treating with phenindione from admission (after hip surgery only, in the first 21 patients) those cases which presented on even dates, and the two series showed good comparability; the difference of 19 patients was not included in the trial because 15, rejected from the treatment series, were thought to be in special danger of bleeding, and 4 patients who should have been in the control series required anticoagulants on admission for miscellaneous reasons. Patients in the control series who developed signs of thrombosis were then given anticoagulants according to the wishes of the surgeon in charge, but in the treated series all patients continued on phenindione until satisfactory walking progress had been achieved, the average period being 5 weeks. Each survivor was followed for three to four months; leg-vein dissections were made *post-mortem* in four-fifths of those dying.

Both in the conduct of the trial and in the analysis of the results the quality of this work is outstanding. A summary of the findings bearing on the value of anticoagulation is reproduced in Table 2, where there is a clear difference in favour of anticoagulants; it is interesting that the two fatal pulmonary emboli in the treated group and seven out of the fifteen in the control group occurred without prior clinical evidence of thrombosis. In addition to the reduction in the occurrence of thrombosis and embolism, the treated group showed a rather shorter mean in-patient stay, 42 days, than the control group, 54 days. From a detailed study of the thromboses occurring in the treated group it was apparent

TABLE 2

Phenindione prophylaxis in fractured femur (188)

Series	Patients	Deaths	Venous Thrombosis		Pulmonary Embolism		
			Clinical	Necropsy	Fatal	Non-fatal	Total
							%
Control.....	150	42	43	29/35	15	12	18
Treated.....	150	25	4	3/21	2	1	2

Of the four clinical thromboses in the treated series, two occurred in patients confined to bed before entering the trial (and in whom there was already some evidence of thrombosis), and two in patients in whom satisfactory anticoagulation was unusually difficult to establish; these patients all survived. The three pulmonary emboli in this group all occurred after the period of anticoagulation.

Fatal emboli included those thought to be wholly or partly responsible for death; the non-fatal group included those clinically so classified, as well as those found at post-mortem which had not been diagnosed during life.

that full protection was afforded only if anticoagulants were begun within two or three days of injury and continued for as long as there might be any danger of thrombosis (approximately one week after reasonable ambulation). In the light of their work on this special group of patients, the authors recommended that prophylactic anticoagulants should be given in general to those over 50 years of age who were about to retire to bed for more than two to three days and who presented no contraindication; they felt that such a policy should reduce by 80 to 90% the incidence of fatal embolism in their hospital.

Chalmers *et al.* (39) studied the yearly incidence of venous thrombosis and pulmonary embolism following gynaecological operations and caesarean section in the United Cambridge Hospitals from 1947 to 1958. These years divide into three periods: the pre-anticoagulant era of early ambulation (2 years), the period of therapeutic anticoagulants (5 years), and finally a trial of prophylactic anticoagulants (5 years). The mean yearly incidence of thrombosis and embolism is given in Table 3.

While the controls for this series of prophylactic anticoagulation were not observed in parallel, the comparisons are probably fair. These workers have been especially interested in thrombosis for the last ten years (126); the data, summarised in Table 3, suggest that the incidence of fatal pulmonary embolism was very steady from 1947 to 1953 and then suddenly fell. It is noteworthy, as this group pointed out before (126), that simply treating diagnosed thromboses (1949–1953) does not affect the incidence of fatal embolism; in fact in Addenbrooke's Hospital alone, the average incidence of fatal pulmonary embolism in medical and surgical wards together was 8.0 per year in 1947–1948 and 10.8 per year between 1949 and 1953: during the latter period 52 of 54 emboli were unheralded and only two occurred in patients in whom crural thrombosis had been diagnosed and who were therefore treated with anticoagulants. In fact, in the hospital group supplying the material for the later study (39), the

TABLE 3

Yearly incidence of thromboembolism following obstetric and gynaecological operations (39)

Period	Measures	Venous Thrombosis	Pulmonary Embolism	
			Fatal	Non-fatal
1947–48	Early ambulation	—	1.3	—
1949–53	Therapeutic anticoagulants	31.8	1.8	4.2
1954–58	Prophylactic anticoagulants	4.8	0.4	1.2

For 1947 and 1948 the records on venous thrombosis and non-fatal embolism were insufficiently accurate for tabulations.

It is stated that between 1947 and 1958, "the number of admissions, the types of case relative to disease, age and operation, and the post-operative care did not appreciably alter."

incidence of fatal emboli confirmed *post-mortem* varied between 0.19 and 0.29 per 100 admissions for medical, surgical, and gynaecological (including caesarean section) cases between 1949 and 1953, and for the first two groups between 1954 and 1958; but in the latter period, in the gynaecological cases who were given prophylactic anticoagulants the incidence fell to 0.04 per 100 admissions. It is clearly on this inescapable incidence of unheralded pulmonary embolism (126, 188) that the case for prophylactic anticoagulants in at least some recumbent patients chiefly rests.

2. In treatment. The general case for the treatment of recumbency thrombosis need not now be reopened, and only one or two points will be made.

While it was stressed above that only to treat diagnosed crural thrombosis will not meet the problem of pulmonary embolism as a whole, it may be that the incidence of embolism as well as duration of morbidity is reduced in the treated group. Thus, Marks and others (126) recorded only three deaths among 1,135 cases of venous thrombosis treated with anticoagulants; however, it is exceedingly difficult to obtain a fair estimate of the expectation of death in similar untreated cases owing to the changing attention to the diagnosis of crural thrombi over the last twenty years.

Barritt and Jordan (12) have investigated the value of initiating anticoagulant treatment after pulmonary embolism has occurred. Cases of sudden death naturally could not be included in the trial (just as they could never be treated), and patients thought unsuitable for anticoagulants were also rejected at the outset (*i.e.*, not only from the treated group). Initially, 35 cases entered the trial and were allocated at random to treated (16 cases) and untreated (19 cases) groups to provide control-in-parallel. On analysis it seemed that treatment was clearly beneficial and it was therefore not felt justifiable to continue the control series; a further 38 cases were therefore all accepted for the treatment group.

Despite the uncertainties of clinical diagnosis (criteria were specified) and of variations in the length of time elapsing between the occurrence of embolism and entering the trial (but within 24 hours in 41 of 73 cases), the results (Table

TABLE 4

Anticoagulant treatment in pulmonary embolism (12)

Series	Patients	Pulmonary Embolism	
		Deaths	Non-fatal recurrences
Control	19	5	5
Treated	54	0	1

Patients were accepted for the trial on making the diagnosis of pulmonary embolus: *i.e.*, embolism had occurred shortly before treatment (or observation) was instituted.

In the initial series of 16 patients treated strictly in parallel with the controls, there were no deaths from embolism, or recurrences.

4) suggest a definite benefit from treatment; severe cases were reasonably distributed between the two groups. The authors were impressed by the survival of every patient who received the first injection of heparin.

E. Cerebral vascular accident

The proposition can obviously be argued that the difficulty in differential diagnosis between the various cerebral vascular accidents makes it unjustifiably hazardous to try to treat cerebral thrombosis or even embolus with anticoagulants, for fear of mistakenly including a proportion of cases of cerebral haemorrhage, despite the engaging *obiter dictum* of one eminent authority that "it doesn't matter treating cerebral haemorrhage with anticoagulants because the brain is all thromboplastin anyway." Indeed, in experimental cerebral embolus with homologous clot fragments, anticoagulants were found to increase the liability to haemorrhagic infarction (194).

Turning to the clinical evidence, Carter (37b) examined the effects of various treatments on cerebral infarction. Taking first embolic cases, he studied 83 patients between 1952 and 1958; Table 5 attempts to analyse the effects of no treatment, stellate ganglion block, and anticoagulants. It appears, first, that there is no striking benefit from multiple stellate block as compared with the untreated group. These two categories are then pooled to provide a "control" group, which is compared with the remainder treated with heparin and phenindione within a week of onset (disregarding the effect of a single stellate block in 15 of the latter group). Of the 34 controls, 32% recovered or improved, whereas of the 49 patients treated with anticoagulants, 67% recovered or improved. This is a significant increase, although of course the cases were not observed in parallel.

A similar study of non-embolic infarction also pointed to some benefit from anticoagulants. For the years 1956 to 1958 a trial in parallel was therefore arranged, taking patients under 70 years of age seen within 48 hours of onset. The diagnostic criteria were that there was no apparent source of an embolus, that the attack was of slow onset and had lasted over two hours, that the diastolic blood pressure was below 120 mm/Hg, and that the CSF was macroscopically

TABLE 5

Anticoagulant treatment in cerebral embolism (87a)

Year	Treatment	Patients		
		Total	Recovered or improved	Died or not improved
1952	Repeated stellate block	16	5	11
1953	Nil	18	6	12
		34	11	23
1954	Single stellate block with anticoagulants	15	11	4
1955 to 1958	Anticoagulants only	34	22	12
		49	33	16

The experience in the patients receiving repeated stellate ganglion block in 1952 was clearly similar to that in untreated patients in 1953, so that these groups have been taken together as a "control" group; the single stellate block used in 1954 has for the same reason been disregarded and these patients pooled with those receiving anticoagulants only, in the period 1955 to 1958, to form an "anticoagulant" group: this manœuvre yields subtotals which may be submitted to Yates' χ^2 test, the result of which suggests ($\chi^2 = 8.55$ on 1 d.f.: $P < 0.01$) that anticoagulants were beneficial.

free of blood. Of 66 such patients admitted to the trial, alternate cases were treated with anticoagulants. The proportion who recovered or improved was 54% in the control group, and 76% in those treated, no more than a suggestive difference (Yates' $\chi^2 = 2.40$ on 1 d.f.; $0.1 < P < 0.2$). Carter thought that anticoagulants were of greatest value in conscious patients with thrombosis of slow onset, where treatment could be begun before the lesion was fully developed: of such cases, 9 of 18 recovered or improved spontaneously, but 16 of 20 recovered or improved on treatment; sudden and complete infarction was unimproved by any treatment.

Marshall and Shaw (126a) carried out a sequential trial of the effect of three weeks' anticoagulation in 51 patients below the age of 70 years, seen within 72 hours of the onset of an acute cerebral vascular lesion thought not to be due to haemorrhage, extra- or subdural haematoma, aneurysm, or arteriovenous malformation, without apparent source of embolus and in whom the CSF was grossly free of blood. The sequential analysis was based on the mortality at six weeks, and the trial was stopped when it was apparent that a preference for anticoagulants could not be obtained; a retrospective analysis of all the material was then carried out after six months' follow-up, and again no benefit from anticoagulant treatment was demonstrated. On the other hand, no "haemorrhagic" infarcts were seen in the treated group *post mortem*, although it appeared that misdiagnosis had led to anticoagulant therapy of three cases of cerebral haemorrhage.

Marshall and Shaw's material appears to be comparable with Carter's non-embolic group; when the data are taken together the evidence for benefit from anticoagulants in such patients must be regarded as still tentative, although Carter's last group (conscious patients, with a lesion of gradual onset still devel-

oping when treatment was started) would seem to be the most hopeful. Nevertheless, as Marshall and Shaw pointed out, it is when the patient is first seen that treatment must be initiated to obtain the greatest chance of benefit, and this is precisely when diagnostic difficulties are greatest. They concluded that anticoagulants could not be recommended for the treatment of most patients with strokes.

In summary, then, the generalization (119a) may be supported that anticoagulants appear to have value in both the prevention and treatment of venous thrombosis, but that their effect on arterial thrombosis is less marked.

III. THE DANGERS OF ANTICOAGULANT THERAPY

Having considered the question, "Do anticoagulants do good?", it is proper next to discuss the corollary, "May anticoagulants do harm?"

The dangers of anticoagulation fall naturally into two groups, the risks of promoting abnormal bleeding and the possibility of other toxic side-effects.

A. Abnormal bleeding

It seems likely that up to a point the frequency of hemorrhagic complications reflects the skill and experience of the physician in charge (162), but it is clear that the definite incidence of bleeding complications in so many published series means that some abnormal hemorrhage must be regarded as an inherent risk of treatment. From the reports tabulated in Peyman's (162) careful study and some others (11, 62, 143a, 241), it would seem that important incidents may be expected in one to ten patients per hundred treated, or some one to five incidents per 100 patient-months.

MacMillan and others (121a) observed eight bleeding episodes in their 27 high-dosage patients in the course of a year, and reported that "several" had given "a few anxious days both for patient and physician."

To be more precise, the occurrence of bleeding will be related to four factors: the skill and vigilance of the doctor, the reliability of the laboratory control, the attention of the patient to the doctor's instructions, and the incidence of potentially haemorrhagic lesions in the patients. The first and second considerations, the principles of administering these drugs and of the control of dosage by laboratory tests, will be considered below; the problem of the rejection of unsuitable patients, which bears on the third and fourth considerations, may conveniently be discussed at this point.

Conditions in which bleeding may be foreseen. Anticoagulants should be withheld from certain patients if there is reason to think that they would be unusually liable to present complications, or if, by circumstances or for reasons of temperament or intellect, they would be unlikely to cooperate fully in their treatment. On the first count, liability to pathological bleeding is of course the major consideration; this has been discussed frequently in recent work. Thus in Bjerkelund's (25) study, local lesions were found which were thought to be at least partly responsible for haemorrhage in 8 out of 21 instances of mild bleeding, in 3 out of 12 of moderate bleeding, and in 7 out of 20 instances of severe bleeding; in Mickerson's (136) series, among 92 patients on phenindione (69 for myocardial

infarction) a pre-existing lesion was thought to determine the site of haemorrhage in 6 out of 7 patients who bled abnormally. In Sevitt and Gallagher's (188) study of anticoagulant prophylaxis in cases of fracture of the femur, 15 patients were rejected from the treatment group because they were thought to be at special risk of bleeding: these included 4 patients with recent symptoms or history of peptic ulcer, 3 with recent bleeding (2 haematemesis, 1 haematuria), 3 with recent hemiplegia, and one each with polycythaemia and recent haemoptysis, bronchectasis with haemoptysis, extensive ecchymosis in the injured thigh, and haemophilia.

In the M.R.C. Working Party's trial (243) of long-term anticoagulants for coronary infarction, patients were rejected because of a history of recurrent haemorrhage, a single haemorrhage within the previous six months, clinical evidence of active peptic ulceration, any other lesion thought likely to lead to bleeding, or any likelihood of intensive salicylate therapy. Nevertheless, the relative risks must always be considered together; a potentially haemorrhagic lesion might be a lesser risk than the coexistent thrombolic disease, and Mickerson (136) found a possible source of bleeding in 35 out of 92 patients on phenindione who did not, in fact, bleed. Curzen (42a) reported a case of coronary infarct with haematemesis managed successfully with intravenous heparin.

The conditions widely regarded as contraindications to anticoagulants, other than the bleeding tendencies or lesions mentioned, may be summarized (162) as comprising severe liver or kidney disease, subacute bacterial endocarditis, emaciation, the immediate postoperative period where there are raw, oozing surfaces, and the period immediately following injury to the central nervous system.

The rejection of patients for reasons of circumstance or temperament is more difficult to categorise; but it is clear that patients must be accessible to the laboratory both for their regular tests and also at short notice if complications arise, that they must be willing to take their drugs as ordered, and also be able to notice and report if signs of bleeding appear or if their state of health materially changes.

It is interesting to note the experience of haemorrhage in three important trials reviewed above, in which care was taken to exclude patients thought unsuitable for the treatment proposed. Bjerkelund (25) recorded 53 episodes (20 severe enough to require readmission to the hospital) in 237 treated cases (total, 22%; severe, 8% or 1 per 21 patient-years; Fuller (62) recorded 1 per 10 patient-years). The M.R.C. Working Party (243) encountered in all 48 haemorrhages among 195 patients (25%) on full dosage compared with 8 among 188 (4%) on token dosage; in the full-dosage group there were 15 withdrawals because of haemorrhage or the risk of haemorrhage; there was one death from bleeding (intracerebral) while on full dosage. After Sevitt and Gallagher's (188) initial screening of their cases, only one patient was withdrawn from the treatment group because of haemorrhage which occurred after anticoagulants had been started, and among the remainder of treated patients (150 cases) there was only one certain and two other possible instances of serious bleeding due to the anticoagulant. What is more interesting still is that operative bleeding was not demonstrably greater in treated than in untreated patients. This point will be discussed below.

Attention must especially be directed to Peyman's (162) study of anticoagulant bleeding, which will be referred to again. It is interesting in this context that Peyman observed 180 patients in the hospital and 34 outpatients on anticoagulant treatment. Besides prothrombin time tests, the orthotolidine tablet test for blood (161) was applied daily to the urine of the inpatients, and the outpatients were taught to perform the test every morning themselves. The results of these tests in relation to gross haemorrhage are shown in Table 6, where it is seen that the association between a positive tablet test and subsequent gross bleeding is relatively low, both for macroscopic haematuria and for bleeding elsewhere in the body. It is our own experience, and no doubt that of others, that small ecchymoses may occur from time to time in treated patients (particularly in the older group) without subsequent serious bleeding. This subcutaneous bleeding perhaps represents a facilitation of the subcutaneous ecchymosis occurring spontaneously in elderly persons and reminiscent of that seen under corticosteroid therapy (117, 182), and thus does not indicate that the anticoagulant treatment has been pushed to the point of producing a general bleeding tendency; neither do such ecchymoses usually lead to the fortunately rare manifestation of haemorrhagic necrosis (73a).

There are various reports of bleeding from special sites. It is remarkable how seldom intracranial haemorrhage has been ascribed to anticoagulant therapy. Of the 58 instances collected by Barron and Fergusson (13), 27 occurred in subacute bacterial endocarditis, and of their own five cases, three were associated with cerebral emboli in rheumatic heart disease and two were in hypertensive patients. Bilateral adrenal haemorrhage giving rise to the Waterhouse-Friderichsen syndrome has also been reported (59); there are occasional reports of fatal haemorrhage in the foetus ascribable to anticoagulant treatment in the mother, but this appears to have been rarer than the theoretical dangers would suggest (51, 68).

In a collected *post-mortem* series (37), cardiac rupture was found more fre-

TABLE 6

Minor haematuria as a warning sign of gross haemorrhage (162)

Patients	Bleeding Episodes	Macroscopic Haematuria		Extrarenal Bleeding		Orthotolidine test positive but no further bleeding
		Orthotolidine test previously		Orthotolidine test previously		
		Positive	Negative	Positive	Negative	
180 inpatients.....	30	4	0	7	10	10
34 outpatients.....	19	0	1	1	11	6
Total.....	49	4	1	8	21	16

Thirty bleeding episodes occurred in 29 inpatients, and 19 episodes in 8 outpatients.

The urine was tested daily for blood by the orthotolidine tablet test (161) in all patients. Thus, of a total of 28 occasions (4 + 8 + 16) when the test was positive, gross bleeding occurred in 12 (4 + 8); gross bleeding presented on 22 occasions (1 + 21) without a previously positive tablet test.

quently in treated than in untreated patients who had suffered acute cardiac infarcts, and attention has been drawn (24) to the autopsy evidence that the incidence of subintimal hemorrhage in the coronary arteries may be more frequent in anticoagulated patients.

Jaques (93) has shown that the incidence of bleeding while on anticoagulants may be increased by simultaneously applying other strains to the haemostatic mechanism, a principle of general interest in the study of haemostasis (21, 88, 175). A special case of this principle is the similarity between the actions of the coumarin and indanedione drugs and large doses of salicylates (135), so that salicylates should not generally be given to patients on these anticoagulants if a reasonable alternative is available. (On the other hand, it has been possible to give anticoagulants and fibrinolytic treatment safely together (140)). The same applies to phenylbutazone and to drugs which interfere with the intestinal flora (216). Of course, if it is necessary to give any of these other drugs, their effect may be judged from changes in the prothrombin time, and the dose of anticoagulant appropriately reduced. Sporadic self-medication is clearly dangerous. Similarly, a risk has been reported in patients already on coumarin-indanedione drugs who are heparinised in preparation, for instance, for open-heart surgery (71).

The danger of haemorrhage from heparin when used alone over longer periods is apparent from the early series in which this was done; a discussion is given by Jorpes (101).

B. Other complications

Phenindione, although generally safe (28), has been associated with agranulocytosis in about a dozen cases (209). Pyrexia has been reported in about the same number (23, 127). Diarrhoea (74, 85, 104, 160) and hepatitis (100) have been reported in about half a dozen, and renal tubular necrosis (12), exfoliative dermatitis (160), and paralysis of accommodation (*qu.* 23) have also been seen. A routine of investigation and management has been suggested by Bingle and Shine (23).

Other coumarin-indanedione drugs have probably not been used so widely as phenindione, so that their relative incidences of non-haemorrhagic complications are difficult to assess. Nevertheless Tashjian and Leddy (209) could find no report up to 1960 of agranulocytosis associated with dicoumarol, tromexan, cyclocoumarol, or warfarin.

Heparin and heparinoids. Toxic reactions occurring with heparin and dextran sulphate have been discussed in detail by Tudhope *et al.* (220). They include alopecia, itching erythema, nail changes, diarrhoea, and thrombocytopenia. Our experience with heparin is that excessive bleeding is a danger only when the drug is continued for more than a week; if heparin is restricted to the first thirty-six hours of anticoagulation, it seems to be well tolerated.

IV. THE ADMINISTRATION OF ANTICOAGULANTS

A. To give or not to give?

Having discussed the evidence for benefit from anticoagulants and the dangers associated with them, the practical issue of their administration to individual patients must now be faced.

In hospital, with adequate laboratory facilities, the decision is relatively unconfused by side-issues. If the patient presents one of the conditions in which there is some evidence of benefit from anticoagulation, and he is free from contraindications, the decision to give anticoagulants will depend on the doctor's estimate of the evidence, such as has been discussed above, that benefit is likely to be obtained.

In domiciliary practice, particularly in the country, circumstances will impose additional considerations. In the first place, more will depend on the patient's ability to follow his instructions exactly, as regards size and frequency of dose, to maintain a stable fat-intake (248), and to report further symptoms of thrombosis as well as abnormal bleeding or other side-effects. Second, it must be possible for the doctor to arrange for blood samples to be taken and conveyed to the laboratory at regular intervals and also at short notice if necessary (if the patient is unable to attend in person), and also to arrange to receive the laboratory report quickly if an urgent change in dose is indicated. Loughridge (116) has recently discussed these problems in detail, explaining how in the course of a year he has cared for a dozen patients on long-term anticoagulation in a mixed urban and rural practice; he described arrangements for the collection of blood samples and the precautions to be taken by ambulant patients. It is important to consider the problems Loughridge raises, because more patients will return to their general practitioners after having been started on long-term anticoagulants in the hospital. As experience is gained, it will be increasingly possible for general practitioners to give anticoagulants for acute thrombotic episodes occurring in patients nursed at home, for it is uneconomical to request hospital admission solely because anticoagulant therapy is indicated. Particularly in acute coronary infarction, when facilities are otherwise adequate at home, the disturbance of moving the patient to the hospital may be definitely harmful, and the possibility of domiciliary anticoagulation is an obvious need; but at present there are strong arguments for hospital treatment in many cases (65). In the face of the rather weak evidence for benefit in coronary infarction, a reasonable policy for both short- and long-term treatment would seem to be to withhold anticoagulants where there is any immediate contraindication, and also in those patients whose condition might be worsened by the incidental measures involved (such as travelling), or in whom there is reason to fear that prolonged, regular medication might induce a cardiac neurosis more disabling than the physical condition. Gillam (65a) has made the interesting suggestion that anticoagulants should be considered most strongly for those patients in whom thrombosis might be thought to play the major part in the development of their disease; in practice, this would mean being more willing to withhold or stop treatment in those presenting with or developing signs of widespread myocardial disease; he suggests that patients should be reviewed six-monthly with this in mind.

B. Dosage schedules

1. The dose of heparin for combined heparin and coumarin-indanedione treatment. The practice of giving heparin in acute cases to cover the initial latent period while coumarin-indanedione drugs take effect is of course well established;

it has been particularly stressed in treating pulmonary embolism (12). Marks *et al.* (126) investigated the necessity of combining heparin with tromexan in this way when treating venous thrombosis, and found that the duration of pain and the length of stay in bed were both shortened when heparin was also given. It is often suggested that heparin should be given intramuscularly. The reviewer has tried to avoid injection of heparin into muscles, since there is evidence from unpublished work on animals that if the tip of the needle happens to lie in an intermuscular septum, a large haematoma may develop between the muscles. Therefore, it is preferable to give heparin intravenously whenever possible, and failing that, deeply subcutaneously away from pressure points: the pectoral regions and the outer sides of the thighs are useful sites. The patient should be instructed to tense the underlying muscles; a large fold of skin and subcutaneous tissue should then be raised and the injection made horizontally into the base of it with a fine needle; in this way the needle will lie superficially to the deep fascia, in the relatively homogeneous subcutaneous fat.

For short-term use, the recommended dose of heparin is 5,000 to 15,000 (usually 10,000) units given 4- to 6-hourly for 18 to 36 hours, commencing with the first dose of the coumarin-indanedione drug. For intravenous use the 5,000 or 10,000 units per ml solution is suitable, but for deep subcutaneous injection a 25,000 units per ml solution is available, of which 0.5 ml may be given. For clinical purposes, 1 mg may be assumed to contain 100 units. Attempts have been made to reduce the risk of hematoma formation by adding 0.1 ml hyaluronidase to an injection of heparin (*not* intravenous), which is said also to reduce local pain (126). Alternatively, heparin has been injected intramuscularly in a waxy menstruum to prolong absorption (228) (a gelatin preparation, Depo-heparin, is also available), and given in conjunction with Coronamide [Carinamide, Staticin, *p*-(benzyl sulfonamido)benzoic acid] to delay excretion (195), although these suggestions do not seem to have been widely adopted. Unfortunately heparin cannot be effectively given by mouth (even sublingually) or rectally (63).

2. The dose of coumarin-indanedione drugs. While of course each of these drugs has its appropriate dose, it is possible to discuss their dosage in general terms. The first few doses are given empirically, and it is important to know the considerations which modify the initial quantities to be prescribed. The relevant factors were carefully studied by the Cambridge group (126) who demonstrated an increasing sensitivity with advancing age (apparent from about 60 years), and described a like effect in heart failure. Using phenindione, and taking the standard initial dose as unity, they (39) gave 0.75 of this dose to patients aged 46 to 55, 0.5 of this amount between 56 and 65 years, and 0.25 of the dose over 65 years of age.

Subsequently, of course, the adjustment of dosage to the requirements of the individual is guided by the prothrombin time test, which is discussed below.

C. The choice of coumarin-indanedione drugs

There are three considerations which govern the choice of an anticoagulant in this group. In practice, the most important consideration is that the doctor should

use the drug with which he is most familiar. All these drugs have much the same effect on the clotting properties of the blood, and differ most obviously in the time-relationships of their actions; hence, it is wise always to use the same drug unless there are good reasons for changing, and then to choose another with a similar rate of action. After this, the next consideration is whether to use a "long-acting" or a "short-acting" drug. With the short-acting drugs, the maximal effect is short; consequently, if an excessive dose is given, the danger of bleeding will be of relatively short duration. On the other hand, the drug will have to be taken twice daily for a smooth effect, and this may lead to occasional doses being omitted by domiciliary patients. Long-acting drugs have the corresponding disadvantage with excessive doses, but since the dose need be taken only at intervals perhaps of several days, some patients may find it easier to cooperate on this basis; if a dose is omitted, the cumulative effect of the drug will partially compensate (217). Toohey (217, 218) sometimes used a short-acting drug (*e.g.*, phenindione or warfarin) for patients in hospital on short-term treatment, and a long-acting drug (*e.g.*, marcumar) for protracted outpatient treatment.

The final consideration is the relative liability of the different drugs to produce toxic side-effects (*i.e.*, other than bleeding). The present evidence perhaps favours the coumarin series, but the discussion (*supra*) has emphasised the rarity of these complications. If such an effect is encountered, the treatment should be changed to another drug of a similar duration of action; *e.g.*, if a toxic manifestation appears during treatment with phenindione, a coumarin derivative could be substituted. For instance, of Borchgrevink's (31) 201 patients initially on phenindione, five developed a rash and two diarrhoea; in each case the symptom subsided when the patient was changed to dicoumarol.

Duration and intensity of action of different drugs. Weiner, Brodie and Burns (234) estimated the length of time taken by various drugs to produce their maximum effect on the prothrombin time, having adjusted the doses to produce the same degree of effect at the peak. Testing each drug in the same five subjects, they found the following single doses to give on the average an equal maximum effect: tromexan, 1.65 g; acenocoumarol, 20 mg; phenindione, 0.4 g; dicoumarol, 0.4 g; marcumar, 24 mg; and diphenadione, 20 mg. The list is in the order of the rate of activity, from the quickest to the slowest; with tromexan and acenocoumarol, the peak effect occurred at about 1½ days, and with marcoumar and with diphenadione, the peaks occurred at about 2½ and 3½ days, respectively, from the time of taking the stated dose. Nichol and others (143a) listed the doses of various anticoagulants used by their group in the treatment of coronary disease, and gave "usual" daily maintenance doses as follows: tromexan, 0.45 g; acenocoumarol, 4 mg; phenindione, 0.1 g; dicoumarol, 75 mg; marcumar, 3 mg; warfarin, 10 mg; and cyclocoumarol, 25 mg. With the exception of marcumar (of which the dose is relatively smaller), these doses are in approximately the same ratios as those given by Weiner, Brodie and Burns, being each one-fourth to one-fifth of their single doses. The relatively lower maintenance dose of marcumar (one-eighth of the latter authors' single dose) reflects the cumulative property of this long-acting drug. Rodman and associates (173) carefully compared the effect

of single doses and the convenience in clinical use of phenindione, dicoumarol, warfarin, and diphenadione; they found the peak effect to occur in that order, over the range of 30 hours to 60 hours, the time of taking the dose of phenindione and of diphenadione, respectively. They found warfarin slightly more easy to use than the others, but the differences between them were not great. Other information on the action of different coumarin derivatives has been given by Shepherd and others (191).

Another indanedione derivative, anisindione, has been introduced (27, 106); the rate of action is similar to phenindione or perhaps a little slower. Like phenindione, it tends to colour the urine red, and patients should be warned to expect this; the colour is bleached by acidifying the urine below pH 4 (159).

Warfarin possesses the valuable feature that a water-soluble sodium salt can be prepared which may be administered intravenously, *e.g.*, in cases of persistent vomiting. Besides this, as an oral drug warfarin has gained favour over phenindione at various centres (134, 189, 217, 218). There are thus short- and long-acting drugs in both the coumarin and indanedione series: *e.g.*, tromexan, warfarin and acenocoumarol as short-, and marcumar as long-acting coumarins, and phenindione and anisindione as short-, and diphenadione as long-acting indanediones. It is thus possible to change to an equivalent drug in the other series if a patient reacts unfavourably to that on which he was started.

D. Other anticoagulants

Attempts have been made to find cheaper substitutes for heparin, and various sulphated polysaccharides have been tested; unfortunately two of the more promising substances, dextran sulphate (220) and Paritol (sodium polyanhydromannuronic acid sulphate) (14) have produced various toxic side-effects and have not been widely accepted. Another interesting departure was the investigation of the anticoagulant properties of the rare earths (particularly neodymium), but unfortunately haemoglobinaemia limited their clinical application (86).

E. Antidotes to anticoagulants

1. For heparin and heparin-like drugs. The classical antidote to heparin is protamine sulphate (41, 158, 163). Recently, Polybrene (hexadimethrine bromide) has been introduced, and seems superior (108, 235). If heparin is used in the treatment of thrombosis simply to cover the initial latent period of the oral anticoagulants, antiheparin agents will very seldom be required, but adequate neutralisation of heparin after extra-corporeal circulation is of the utmost importance. In this context Polybrene has been found particularly useful, and a distinct improvement over protamine sulphate (178). Toluidine blue would also seem to be less suitable in this connection (178a, 204).

2. For coumarin-indanedione drugs. The antidotes to this group of drugs are found in the vitamin K series, although the exact relationship is somewhat complicated.

In chicks, a K-deficient diet potentiated the action of dicoumarol, and K_1 (mephyton, phytonadione, the naturally-occurring vitamin) and menadione

(menaphthone, 2-methyl-1,4-naphthoquinone) appeared equally effective in counteracting this drug (169). In the dog, K-deficiency induced by cholecystnephrostomy similarly increased the prothrombin time response to dicoumarol, but the effectiveness of members of the K-series as anti-dicoumarols was in the order K_1 first, hykinone [2-methyl-1,4-naphthohydroquinone, 3-sodium sulphonate] and synkavite [2-methyl-1,4-naphthohydroquinone diphosphoric ester tetra sodium salt] about equal as second, and menadione last. In normal man, menadione derivatives can shorten the prothrombin time below normal (224), and menadione is very effective in treating the haemorrhagic disease of the newborn (1, 122); yet these water-soluble K-analogues are very much less effective (46) than the naturally-occurring K_1 in reversing the effects of coumarin-indanedione drugs in man; K_1 is extremely active in this respect (105). Radio-isotope studies in the rat have shown (210) that vitamin K_1 diffuses freely into many tissues and passes the placental barrier to be distributed in the foetus; it was also found that the vitamin was considerably concentrated in the liver, in contradistinction to K_3. It is clear, therefore, that vitamin K_1 is the appropriate antidote in man. A further problem arises, however, in deciding the appropriate dose. First, this substance can be given by mouth or intravenously; by the latter route its action is the more rapid, as might be expected. Secondly, the effect of a larger dose is more rapid than that of a smaller; but after a large dose the patient will show prolonged refractoriness (of the order of days to weeks) to further doses of anticoagulant. It has also been thought that too rapid or complete a reversal of the anticoagulant effect may precipitate further thrombosis, but the evidence is unclear (43). The possible dose range is from 2 to 5 mg by mouth to 50 to 100 mg intravenously, but the higher doses will seldom be required: Toohey regarded 20 mg as the practical upper limit (216). The appropriate dose is the smallest which will achieve the necessary degree of reversal of anticoagulation in the time available. The obvious course is to determine the prothrombin time as soon as the need for the antidote is apparent, then to give the smallest dose thought reasonable, and to repeat the determination of the prothrombin time after a suitable interval. Oral administration is usually satisfactory, but a more rapid effect is achieved by intravenous injection; after an intravenous dose in a fit person the prothrombin time should begin to shorten in four to six hours. If the second test shows an insufficient effect, more K_1 can then be given. If the patient is to be anticoagulated again as soon as the emergency is over, the dose of K_1 should obviously be smaller than if anticoagulants are to be withdrawn altogether.

It has generally been thought wise to reverse the action of anticoagulants in patients about to undergo surgery or dental extraction (*e.g.*, M.R.C. Working Party, 243), but this view has recently been challenged. Toohey (216) found that emergency, including major, surgery could be performed with only a reduction and not complete withdrawal or reversal of anticoagulation; in Sevitt and Gallagher's (188) series of fractured femur cases treated with phenindione, hip operations were carried out under full treatment with no more bleeding than in the controls. Similar experiences in several surgical series have been summarised by I. S. Wright (251a). However, it may be that bleeding from serous surfaces (215)

is a real danger in the immediate postoperative period where the extent of the operation makes this likely.

It has also been felt that K_1 should be given if by accident the prothrombin time is raised above some defined excessive value, even if the patient does not bleed excessively. This may be wise with the long-acting anticoagulants, but the reviewer has not thought it necessary with phenindione, at any rate for patients in hospital; he gives K_1 only if the patient begins to bleed, knowing that otherwise simply withdrawing the anticoagulant will allow the prothrombin time to fall again over the next day or two and no harm may come. It is considered easier to regain control of the dosage in this way without the added complication of giving an antagonist. If bleeding occurs (*e.g.*, haematuria), K_1 can be given intravenously without delay. It may be wise to supply outpatients (especially those on long-term treatment) with one or two oral capsules of K_1 to take if they have the misfortune to be involved in an accident, and with a card to carry recording the fact that they are on treatment, to warn a surgeon who might be involved with an emergency operation following an accident, particularly if the patient should be unconscious.

V. THE CONTROL OF ANTICOAGULANTS

A. Heparin

It has already been stated that for the brief initial use of heparin to cover the latent period of the coumarin-indanedione drugs, heparin can be given empirically. If it is thought necessary to check that the patient is adequately heparinised at any given moment, the whole-blood clotting time is an adequate test: if the result is prolonged over the control by approximately twice or more, the patient's blood can be taken to contain heparin at that time; however, it is not accurately known by how much the clotting time should be prolonged to ensure adequate anticoagulation. Perhaps the necessary degree of effect varies with different thrombotic conditions.

The importance of adequate neutralisation of heparin at the end of open-heart operations has also been stressed above. Rothnie and Kinmonth (178) used the thrombin clotting time test (30, 94, 171), with the addition of toluidine blue as a confirmatory procedure. This test is simpler than protamine titration (114) or separation procedures (60), and is more convenient than whole-blood tests (2, 96). The sensitivity of the test can be adjusted by varying the potency of the thrombin reagent, and the test can be readily adapted as an assay of circulating heparin (92).

B. Coumarin-indanedione drugs

Chemical estimations for the concentrations of these drugs in body fluids are available (137, 174, 226) but, aside from their use in forensic work, are not of direct help in the control of treatment, except when there is real doubt whether the patient has taken the drug at all or if for some reason the haematological evidence is equivocal (226).

1. Principles of control. An ideal test for the control of these drugs should take

account of their two-fold activity: the procedure should indicate the optimum dosage for benefiting the thrombotic condition and also give warning of incipient bleeding from overdose. It is widely realised that current tests fall short of this ideal (16, 196), and close attention is therefore needed in their application.

While the backbone of control is Quick's prothrombin time or one of its derivatives, this may be augmented by other clotting tests, such as the heparin-retarded clotting time or thromboelastography. In addition, other techniques may be applied, such as tests of capillary fragility and for microscopic haematuria. The clotting tests will indicate, at least in theory, whether anticoagulation is adequate and will point as well to excessive dosage; whereas the other tests are only intended to reveal incipient overdose.

2. The prothrombin time test (Quick's method). The history of this test has been given in the introduction. It is extremely simple to perform, has a low experimental error (7, 89), and the variation among normal persons is small (90); the test is very widely used and generally known. Local results may be expected to be consistent over periods of time comparable with the duration of long-term treatment in individual patients, and results between different centres are reasonably comparable (243). Technical considerations, such as the optimum calcium concentration (95) and the effect of differences in the sources (211, 225) or methods of preparation (126, 164) of the tissue reagent, have been carefully studied.

Attempts to improve on this test have nevertheless been made in several directions.

3. Modified Quick tests. Minor modifications are often introduced, such as to reduce the number of pipetting operations by premixing the tissue reagent and the calcium chloride solution (107) or to use fresh, whole blood instead of citrated plasma (213). It has also been felt that a more convenient "accelerator" than tissue extract could be found; attempts were made to use Russell's viper venom, with or without the addition of lecithin (82), but for the control of anticoagulants the test was found to be less sensitive than with tissue extract (130), perhaps because by this modification the technique is insensitive to a reduction of factor VII (98).

The necessity to perform venepuncture has been widely regarded as a disadvantage, and a number of modifications have been suggested to allow the test to be made on a small quantity of capillary blood obtained from a finger- or earpuncture (121, 124). These tests have been carefully discussed by Stein (205); but have not been generally accepted, perhaps because it is felt to be more difficult to handle very small volumes sufficiently accurately.

In an attempt to increase the sensitivity of the procedure, the plasma was diluted (often to 1 in 8) in saline before being added to the test (190). While a dilution of the clotting factors affected by the anticoagulant might reasonably be expected to sharpen the discrimination of the technique, the concomitant dilution of all other constituents of the plasma might have had undesirable effects, and interpretation was difficult.

4. The "P & P" test and "Thrombotest." It is also possible that incidental changes in other clotting factors might irrelevantly modify the test results. For

instance, relatively small changes in fibrinogen concentration or factor V might influence the prothrombin time test but not the haemostatic mechanism in the patient; conversely, they might be such as to mask real changes in the haemostatic mechanism induced by the anticoagulant. To avoid perturbations such as these, Owren and Aas (155) introduced the "P & P" test, so called because it was thought to reflect accurately the combined changes in prothrombin and proconvertin (factor VII), the two clotting factors known at that time to be reduced by coumarin-indanedione drugs. In this method, the patient's and the control oxalated plasma are diluted 1 in 10 in oxalated veronal buffer and mixed in equal volumes with asbestos-filtered bovine plasma and brain reagent; the bovine plasma supplies fibrinogen and factor V but the asbestos-filtration greatly reduces its content of prothrombin and factor VII (and, as we now know, of factor X). The mixture is recalcified and the clotting time determined in the usual way.

In this method, the preliminary dilution affected only the final concentration of clotting factors thought to be relevant, and hence it seemed meaningful to record P & P values above 100%. An additional advantage of the procedure was that a small quantity of heparin might be added to the anticoagulant with which the blood was initially mixed, which was thought to stabilise the clotting factors in the sample in the interval between venepuncture and performing the test; by this means blood samples could be sent to the laboratory by post. The subsequent dilution of the plasma would then reduce the heparin concentration below that critical for the test. It was later found that this method enabled control of anticoagulant dosage to be achieved rather more rapidly than with Quick's test; certainly in Owren's hands the test has been very satisfactory, and in particular it has justified (20, 31) his hope (155) that bleeding complications might be reduced.

Nevertheless, when it became apparent that factor IX (the Christmas factor) was reduced by these drugs, Owren further modified his test to be sensitive to reductions in this factor also. He (150) prepared an "all-in-one-reagent," called "Thrombotest," containing phospholipid from human brain or soya bean, a crude extract of bovine or equine brain, adsorbed bovine plasma, and calcium chloride. The quantities of the first and second components were so adjusted that in normal plasma the phospholipid and the crude brain extract led to the activation of "blood" and "tissue" thromboplastin at about the same rates, so that the endpoint of the test should reflect more or less equally the activities of factors VII, IX, and X. The adsorbed bovine plasma ensured that alterations in the patient's factor V or fibrinogen should not influence the test. The Thrombotest was shown to be as sensitive as the P & P method to changes in factor VII and more sensitive to changes in factor IX, as had been intended. The test could equally be made on venous or capillary blood, and was suitable for testing specially heparinised postal samples. A minor disadvantage was that samples to be tested after an interval from collection had to be taken into non-wettable containers, since the test was accelerated to some extent by glass-contact, but this was not serious because various disposable plastic tubes were satisfactory.

Nour-Eldin (144, 145) doubted the claim that the Thrombotest was sensitive to changes in factor IX, and reported normal or near-normal values in patients

with Christmas disease. However, it might well be that the sensitivity of the procedure to factor IX is heightened by concurrent depressions of other factors, as would be expected in anticoagulant treatment (113), and Owren himself later (153) substantiated this. British workers who have tried the new test have been impressed with its possibilities (4, 113a, 129), although it was pointed out that the Thrombotest was rather more sensitive than the P & P method to the heparinaemia of the first few days of combined treatment. Initial reservations about the cost of the test are being met in various ways (61, 154, 154a). A particular advantage of the Thrombotest is that it can be conducted during the period of an office visit.

5. Other clotting tests. A number of other tests have been used from time to time. For instance, some workers have concentrated on an estimate of prothrombin itself, either by the classical "two-stage" method or a modification of this (230, 232) or by the "stabilised thrombin" (206) or the TAMe (*p*-toluenesulfonyl-1-arginine-methyl ester) techniques (3, 159). It is not clear that the clinical results have been significantly better than by the more usual procedures.

At one time it was thought (201, 202) that the heparin-retarded clotting time would give a better over-all indication of the coagulability of the blood than the Quick tests. However, there does not appear to be good evidence that better clinical results are obtained, and the test is less easy to standardise than the prothrombin time.

It has been suggested that a test using 2.5% sodium chloride solution might usefully complement the P & P test (227); but perhaps the place of this procedure is now adequately filled by the Thrombotest. Lastly, the thromboelastograph has also been used for anticoagulant control (240), but however elegant, so expensive an instrument has its own limitations for a very wide-spread problem like anticoagulation.

6. Other types of test. A routine test for microscopic haematuria was tried by Peyman (161, 162), to detect the onset of a dangerous tendency to bleed; as mentioned above, the results were rather disappointing: some patients gave a positive test without subsequent serious bleeding, while other patients who bled from other sites or who presented gross hematuria had given no warning in the test. Peyman (162) also tried a capillary resistance test, but was unable to establish abnormal results in treated patients, either in those who bled or in those who remained free of bleeding.

The bleeding time appears to be a little prolonged under anticoagulant treatment (227), but it would be somewhat impractical to control dosage with a rather unpleasant test which requires multiple punctures to achieve fair accuracy.

7. Comparisons between different tests. Toohey (219) compared Quick's test with the P & P method and with Ware's modification (231) of this test, over a large number of routine blood samples, and concluded with a preference for the P & P method for inpatients, because of its more rapid reflection of changes in the blood, and for Quick's method for outpatients. He gave a number of technical details. Extensive scatter-diagrams correlating Quick's test with a number of others were given by Verstraete, Vermylen and Vandenbroucke (227). The correlation be-

tween the P & P method and the Thrombotest, discussed in several of the references given under that heading, has been found to be close (156). Owren was quoted (31) as having found that the correspondence between Quick's test and the P & P test (and hence by implication, the Thrombotest) depends on the type of tissue extract used in the Quick technique. If acetone-dried rabbit brain is used, a prolongation of 2 to 2½ times the control time by this method corresponds with 7 to 15% by the P & P method; with human brain the corresponding P & P range is 10 to 20%, with Symplastin it is 17 to 24%, and with Soluplastin 20 to 30%. (Symplastin and Soluplastin are proprietary tissue extracts of the type used in the prothrombin-time test.) Lempert and Poller (113a) correlated the Quick, P & P, and Thrombotest methods with the thromboplastin generation test. The results by various techniques regarded as representing equal therapeutic effects have been tabulated by Duff and others (48).

The relationship of the Quick test to changes in particular clotting factors has also been mentioned above. Further information has been given by Sise and others (196) and by Hicks and Bonnin (80) who found that if the Quick test clotting time was greater than about 1.5 × the control time, all the clotting factors affected by the anticoagulants would usually be well below normal levels.

Despite the contrary advice of eminent workers, the Quick test continues to be widely used. The reviewer finds this technique satisfactory, and feels that the extreme simplicity both of reagents and method ensures a comparability of results over long periods of time, and in the hands of a succession of medical and technical laboratory personnel, which more involved tests might sacrifice.

8. Expression of results. The early attempts to express Quick test clotting times in terms of concentrations of clotting factors have been steadily abandoned, and are now retained only as a convenient and familiar convention where their use has become traditional. It is probably best to report the control clotting time, the patient's clotting time, and the ratio between the two (patient's time/control time). For the P & P and Thrombotest techniques, on the other hand, it is simplest to follow Owren's system of "percentages" even if judgement is reserved as to their precise meaning.

9. Intensity of treatment. The above remarks introduce the important and controversial matter of how vigorously anticoagulant treatment should be pressed so as to steer the best course between the maximum protection against thrombosis and the dangers of abnormal bleeding. For many years there was little exact information available (40), but recently some important data have been published.

One might have expected that this problem could be approached by experiments in animals. Unfortunately, as was mentioned, much of the work has been rather remote from the clinical situation, but there is one recent experiment which may be helpful. Carey and Williams (37a) induced localised thrombosis electrically in the external jugular vein of the dog, and then studied the subsequent spontaneous *extension* of the thrombus, which would seem reasonably similar to the extension of a natural thrombus in man. If not dislodged, in 48 hours these thrombi propagated to several times their original length (8 dogs), but this was prevented (7 out of 8 dogs) by 8-hourly injections of heparin (beginning immediately after the thrombus was established), maintaining the blood-

clotting time 2 to 3 times prolonged. Eight other dogs were stabilised on dicoumarol before the induction of the thrombus, but propagation occurred in all except the one dog, the prothrombin time of which was prolonged to a degree recorded as "less than 10%" (in the others, three levels were between "20%" and "30%," and four between "10%" and "20%"). In four dogs given tromexan the levels were "below 20%," but the clots propagated in two. There were signs of overdose bleeding, sometimes severe, with levels "below 20%." This work confirms the clinical impression that heparin is the more powerful antithrombotic agent, and supports the principle of giving the highest tolerated dose of the coumarin-indanedione drugs.

In man, Peyman (162) has made a special study of this problem. Using Quick's test, he closely followed 180 inpatients and 34 outpatients treated with coumarin anticoagulants. He listed in detail the haemorrhagic and thrombotic incidents occurring during treatment, and gave the patients' prothrombin times over the immediately preceding period in each case. Among the inpatients there were ten, and among outpatients two further thrombotic incidents: in no case did the immediately preceding prothrombin time exceed twice the control time. On the other hand, in 23 of 30 bleeding incidents in inpatients and in 15 of 19 bleeding incidents in outpatients, the immediately preceding prothrombin time had been three or more times the control time. This suggests that the appropriate therapeutic range is about two-and-a-half times to three times the control value.

Borchgrevink's (31) important study of two groups of coronary patients, controlled by the P & P test at about 50% and 20% of the control activity, has been discussed in detail above. There was a clear difference between both infarction rate and mortality, the 20% group (*i.e.*, the *more* vigorously treated) having the advantage on both counts. Haemorrhage occurred in 10 out of 103 patients in the 20% group (one haemorrhage per 14.2 patient years) and in 1 out of 100 patients in the 50% group. In seven (P & P values 55% to less than 5% at the time of bleeding) a predisposing cause was diagnosed; in the four others (P & P values 8% to less than 5%) no cause was found. In discussing this work, Owren (151) suggested that the old concept of a "therapeutic range" is illusory: perhaps the more logical attitude is to give each patient the highest dose which he can tolerate without bleeding; however, this brings the argument back to the problem of how to foresee haemorrhage. Owren admitted that for practical purposes patients should be maintained in the range below 25% by the P & P or Thrombotest, although rather more latitude is allowed in the published description of the latter (150), where the therapeutic range is given as 10 to 30%.

Notes on relating the succeeding dose of oral anticoagulants to the immediately preceding prothrombin time have been given by Toohey (218) for warfarin and by Barritt and Jordan (12) for nicoumalone. There is a detailed, general discussion of the control of anticoagulants in large groups of patients by Owren (152); and Duff and others (48) have particularly considered the problems of avoiding overdosage. Lempert and Poller (113a) associated bleeding especially with a reduction in thromboplastic factors, and felt that the Thrombotest is useful in avoiding overdose, by virtue of its sensitivity to factor IX.

Despite every care, however, some patients will experience further thrombotic

episodes under treatment. Recurrent migratory phlebitis resistant to anticoagulants has been regarded as strongly suggesting a hidden carcinoma (223).

10. Frequency of testing. In the acute phase, and at the start of treatment, many centres estimate the prothrombin time daily. Prothrombin times should not be started until the initial heparin coverage has been eliminated, since this will affect the test (19); therefore, the heparin doses should be so arranged that the first test can be made about 36 hours after starting a short-acting drug by mouth. (The reviewer allows four to five hours to elapse after the last intravenous injection of heparin and about twenty-four hours after the last deep subcutaneous injection, before taking the first blood sample).

It is true that even with Quick's test, daily changes can be expected in patients taking the short-acting drugs (128), but the full effects of a change in dosage may not be seen until the second day; the reviewer is therefore satisfied with tests on alternate days for the first week, and thrice or twice weekly thereafter until the appropriate dose has been found, after which inpatients are commonly tested once a week or so. The frequency of testing outpatients depends on the stability of their response, which may vary widely between patients, and even from time to time in the same person (148); whereas some centres (217) may allow as much as 2 to 3 months between outpatient tests, others (148) feel that 2 weeks should never be exceeded.

VI. SUMMARY

Anticoagulant drugs have been considered in their clinical rather than their experimental context, for it is the problems of the assessment of therapeutic effect and of the control of dosage which are now being most keenly discussed. Space has been devoted to the evidence for therapeutic benefit in different thrombotic conditions, and to the practical difficulties which may be encountered. The control of dosage has been discussed in some detail, and an integration of the clinical and laboratory problems has been attempted. These, of course, are concerns which have attracted the attention of many able people, to only a fraction of whose work has it been possible to refer.

Good evidence has been found to support the value of anticoagulants in venous thrombosis, but their effect on arterial thrombosis is less marked. Routine administration to patients with fractured femur led to a marked reduction in the incidence of venous thrombosis and of embolism; a similar result was obtained after obstetric and gynaecologic surgery. The treatment of established venous thrombosis did not eliminate pulmonary embolism, but did reduce the morbidity of the primary thrombosis. Nevertheless, even after pulmonary embolus had been diagnosed, anticoagulant treatment reduced the immediate mortality and the danger of recurrence. In the chronic stage of rheumatic heart disease the incidence of thromboembolic episodes was much reduced. In coronary artery disease and myocardial infarction definitive studies have proved difficult to set up, owing to the number of factors which influence prognosis and which therefore have to be controlled; the evidence is incomplete but suggests that some benefit may be expected. In the acute phase, at least a reduction in secondary thrombosis

seems established; and long-term treatment may somewhat reduce the mortality. In peripheral arterial disease the effect on the arterial lesions is dubious.

Overdose bleeding may be reduced by withholding anticoagulants from patients with local lesions liable to bleed. Minor haematuria or provoked purpura ("capillary fragility" tests) are of little value as warning signs of major bleeding. Surprisingly, the coumarin-indanedione drugs do not greatly impair surgical haemostasis. Side-effects other than bleeding seem to be rare with either coumarins or indanediones, but perhaps a little more frequent with the latter.

The development of Quick's test and of Owren's "P & P" and "Thrombotest" is described and their relative merits are discussed. The Quick test is still being found satisfactory in many hospitals but the Thrombotest would seem to have definite advantages under certain circumstances.

The reviewer has thus aligned himself soberly with the enthusiasts for anticoagulant treatment; but he remains conservative in continuing to use Quick's one-stage prothrombin time test for control.

ACKNOWLEDGMENTS

I should like to thank Professor P. Owren and Messrs. Nyegaard and Co., A/S, Oslo, Norway, for permission to reproduce Figures 1 to 3; Dr. C. F. Borchgrevink, for putting his results at my disposal in advance of publication (ref. 31); Dr. G. A. Carnachan of Evans Medical Ltd., Liverpool, England, for certain references; and C. W. Peck, Esq., F.P.S., Pharmacist to St. Thomas's Hospital, London, England, for his advice on the names of drugs. I am very grateful to Miss D. Burridge for the typescript.

REFERENCES

1. Aballí, A. J., Banús, V. L., de Lamerens, S. and Rozengvaig, S.: Coagulation studies in the newborn period. J. Dis. Child. 97: 524–548, 1959.
2. Adams, S. S. and Smith, K. L.: The use of sulphated whole blood in the assay of heparin. J. Pharm., Lond. 2: 836–846, 1950.
3. Alexander, F., Koppel, J. L., Arscott, P. M. and Olwin, J. H.: Clinical experience with the anticoagulant Acenocoumarin (Sintrom). Arch. intern. Med. 100: 558–564, 1957.
4. Allington, M. J.: Thrombotest method for the control of anticoagulant therapy. Lancet 1: 224–225, 1960.
5. Alrich, E. M.: Studies on burns. III. The effect of heparin on the circulating blood plasma and proteins in experimental burns. Surgery 25: 677–680, 1949.
6. Anderson, N. G. and Fawcett, B.: An antichylomicronemic substance produced by heparin injection. Proc. Soc. exp. Biol., N. Y. 74: 768–771, 1950.
7. Armitage, P. and Ingram, G. I. C.: Studies in the variability of two blood-clotting tests. Appl. Statistics 7: 1–14, 1958.
8. Aschoff, L.: Lectures on Pathology, pp. 253–278 (chap. XI: Thrombosis). Hoeber, New York, 1924.
9. Astrup, T. and Darling, S.: Antithrombin and heparin. Acta physiol. scand. 5: 14–30, 1943.
10. Bannister, R. G.: The risks of deferring valvotomy in patients with moderate mitral stenosis. Lancet 2: 329–332, 1960.
11. Barker, N. W., Cromer, H. E., Hurn, M. and Waugh, J. M.: The use of dicumarol in the prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration. Surgery 17: 207–217, 1945.
12. Barritt, D. W. and Jordan, S. C.: Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. Lancet 1: 1309–1312, 1960.
13. Barron, K. D. and Fergusson, G.: Intracranial hemorrhage as a complication of anticoagulant therapy. Neurology 9: 447–455, 1959.
14. Beazley, H. L., Foster, W. J., Ory, A. A. and Chapman, D. W.: The effect of intravenous and intramuscular Paritol on the clotting time. Amer. J. med. Sci. 226: 275–280, 1953.
14a. Benditt, E. P.: Actions of heparin other than those on coagulation. Annu. Rev. Med. 8: 407–414, 1957.
15. Best, C. H., Cowan, C. and MacLean, D. L.: Heparin and the formation of white thrombi. J. Physiol. 92: 20–31, 1938.

16. Biggs, R.: The laboratory control of anticoagulant therapy. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 774–783. Schwabe, Basel, 1955.
17. Biggs, R.: Some observations on the blood of patients with 'factor-VII' deficiency. Brit. J. Haemat. 2: 412–420, 1956.
18. Biggs, R. and Douglas, A. S.: The measurement of prothrombin in plasma. J. clin. Path. 6: 15–22, 1953.
19. Biggs, R. and Macfarlane, R. G.: Estimation of prothrombin in dicoumarin therapy. J. clin. Path. 2: 33–44, 1949.
20. Biggs, R. and Macfarlane, R. G.: Human Blood Coagulation and Its Disorders. 2nd ed., Blackwell Scientific Publications, Oxford, 1957.
21. Biggs, R. and Macfarlane, R. G.: Haemophilia and related conditions: a survey of 187 cases. Brit. J. Haemat. 4: 1–27, 1958.
22. Bingham, J. B., Meyer, O. O. and Pohle, F. J.: Studies on the hemorrhagic agent 3,3'-methylenebis(4-hydroxycoumarin). I. Its effect on the prothrombin and coagulation time of the blood of dogs and humans. Amer. J. med. Sci. 202: 563–577, 1941.
23. Bingle, J. and Shine, I.: Phenindione sensitivity. Lancet 2: 377–379, 1959.
24. Biss, K.: Subintimal hemorrhage in coronary arteries in cases treated with anticoagulants. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 1108–1112. Schwabe, Basel, 1955.
25. Bjerkelund, C. J.: The effect of long term treatment with dicoumarol in myocardial infarction: a controlled clinical study. Acta med. scand. 158: suppl. 330, 1957.
26. Blake, O. R., Ashwin, J. G. and Jaques, L. B.: An assay for the antithrombotic activity of anticoagulants. J. clin. Path. 12: 118–122, 1959.
27. Blaustein, A.: A preliminary report on the clinical use of a new anticoagulant (Miradon). N. Y. St. J. Med. 58: 701–702, 1958.
28. Blaustein, A., Shnayerson, N. and Wallach, R.: Clinical use of a new anticoagulant, phenylindanedione: report of 400 cases. Amer. J. Med. 14: 704–706, 1953.
29. Block, W. J., Jr., Crumpacker, E. L., Dry, T. and Gage, R. P.: Angina pectoris. Observations in 6,882 cases. J. Amer. med. Ass. 150: 259–264, 1952.
30. Blombaeck, M., Blombaeck, B. and Wallén, P.: Détermination du taux de l'héparine dans le sang en cas de circulation extra-corporelle au cours de la chirurgie cardiaque. Rev. Hémat. 10: 45–54, 1955.
31. Borchgrevink, C. F.: Long-term anticoagulant therapy in angina pectoris and myocardial infarction. A clinical trial of intensive versus moderate treatment. Acta med. scand. 1960, suppl. 359.
31a. Borchgrevink, C. F. and Waaler, B. A.: The secondary bleeding time. A new method for the differentiation of hemorrhagic diseases. Acta med. scand. 162: 361–374, 1958.
32. Bounameaux, Y.: Recherches sur les facteurs de l'adhésivité des plaquettes in vitro. Actes du 1er Symposium de la Fondation Valentino Baldacci, Madrid, 27–30 Mai, 1955, pp. 40–61. Omnia Medica, Pisa, 1955.
33. Brown, W. D.: Reversible effects of anticoagulants and protamine on alimentary lipæmia. Quart. J. exp. Physiol. 37: 75–84, 1952.
34. Burt, C. C., Wright, H. P. and Kubik, M.: Clinical tests of a new coumarin substance. A report to the Medical Research Council. Brit. med. J. 2: 1250–1254, 1949.
35. Butt, H. R., Allen, E. V. and Bollman, J. L.: A preparation from spoiled sweet clover [3,3'-methylene-bis(4-hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood: preliminary report of experimental and clinical studies. Proc. Mayo Clin. 16: 388–395, 1941.
36. Campbell, H. A., Smith, W. K., Roberts, W. L. and Link, K. P.: Studies on the hemorrhagic sweet clover disease—II. The bioassay of hemorrhagic concentrates by following the prothrombin level in the plasma of rabbit blood. J. biol. Chem. 138: 1–20, 1941.
37. Capeci, N. E. and Levy, R. L.: The influence of anticoagulant therapy on the incidence of thromboembolism, hemorrhage and cardiac rupture in acute myocardial infarction. Amer. J. Med. 26: 76–80, 1959.
37a. Carey, L. C. and Williams, R. D.: Comparative effects of dicoumarol, tromexan and heparin on thrombus propagation. Ann. Surg. 152: 919–922, 1960.
37b. Carter, A. B.: Immediate treatment of cerebral infarction: seven years' personal experience. Lancet 1: 345–351, 1960.
38. Cejka, V., de Vries, L. A., Smorenberg-Schoorl, M. E., van Daatselaar, J. J., Borst, J. G. G. and Majoor, C. L. H.: Effect of heparinoid and spirolactone on the renal excretion of sodium and aldosterone. Lancet 1: 317–319, 1960.
39. Chalmers, D. G., Marks, J., Bottomley, J. E. and Lloyd, O.: Postoperative prophylactic anticoagulants: five-year study in an obstetric and gynaecological unit. Lancet 2: 220–222, 1960.
40. Coon, W. W., Mackenzie, J. W. and Hodgson, P. E.: A critical evaluation of anticoagulant therapy in peripheral venous thrombosis and pulmonary embolism. Surg. Gynec. Obstet. 106: 129–136, 1958.
41. Cowley, L. L. and Lam, C. R.: The neutralisation of heparin by protamine. Surgery 24: 97–99, 1948.
42. Crafoord, C.: Preliminary report on postoperative treatment with heparin as preventive of thrombosis. Acta chir. scand. 79: 407–426, 1937.
42a. Curzen, P.: Management of acute myocardial infarction complicated by haematemesis. Brit. med. J. 2: 1489–1491, 1960.
43. Dedichen, J.: Long-term anticoagulant therapy in cardiovascular disorders with phenylindanedione. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 1112–1114. Schwabe, Basel, 1955.
43a. Dinon, L. R. and Vander Veer, J. B.: Recurrent myocardial infarction after cessation of anticoagulant therapy. Amer. Heart J. 60: 6–22, 1960.

44. Donner, W. M.: Neue Ergebnisse der kombinierten Behandlung mit Antikoagulantien und Röntgenstrahlen. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 1200–1204. Schwabe, Basel, 1955.
45. Douglas, A. S.: Antihemophilic globulin consumption during blood coagulation. Blood 11: 423–429, 1956.
46. Douglas, A. S. and Brown, A.: Effect of vitamin-K preparations on hypoprothrombinaemia induced by dicoumarol and tromexan. Brit. med. J. 1: 412–415, 1952.
47. Douglas, A. S. and Mair, K.: The Christmas factor deficiency in coumarin therapy. Clin. Sci. 17: 445–455, 1958.
48. Duff, I. F., Gamble, J. R., Willis, P. W., Hodgson, P. E., Wilson, W. S. and Polhemus, J. A.: The control of excessive effect by anticoagulants. Ann. intern. Med. 43: 955–978, 1955.
49. Duncan, C. H., Best, M. M. and McGaff, C. J.: Clearing system for blood fats stimulated by a heparinoid. Lancet 1: 1014–1015, 1959.
50. Eberth, C. J. and Schimmelbusch, C.: Die Thrombose nach Versuchen und Leichenbefunden, chap. 4. Stuttgart, 1888.
51. *Editorial*: Dangers of dicoumarol. Brit. med. J. 2: 1279–1280, 1949.
52. Elrod, P. D., McCleery, R. S. and Ball, C. O. T.: An experimental study of the effect of heparin on survival time following lethal burns. Surg. Gynec. Obstet. 92: 35–42, 1951.
53. Ensor, R. E. and Peters, H. R.: Long-term anticoagulant therapy in coronary disease. J. Amer. med. Ass. 169: 914–918, 1959.
54. Feissly, R. and Enowicz, M.: Héparine et coagulation du sang. Schweiz. med. Wschr. 76: 274–279, 1946.
55. Foley, W. T., McDevitt, E., Symons, C. and Wright, I. S.: Further experience with long-term anticoagulant therapy. Arch. intern. Med. 95: 497–502, 1955.
56. Foley, W. T. and Wright, I. S.: Long-term anticoagulant therapy for cardiovascular diseases. Amer. J. med. Sci. 217: 136–142, 1949.
57. Foley, W. T., Wright, I. S., McDevitt, E. and Symons, C.: A study of 85 patients on long-term anticoagulant therapy for one year or more. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 1102–1108. Schwabe, Basel, 1955.
58. Forwell, G. D. and Ingram, G. I. C.: The anticoagulant activity of dextran sulphate. I. An *in vitro* comparison between the actions of dextran sulphate and heparin in the various stages of blood coagulation. J. Pharm., Lond. 8: 530–543, 1956.
59. Fragge, R. G., Bernstein, I. L. and Bell, J.: Fatal "Waterhouse-Friderichsen Syndrome" due to dicumarol. Ann. intern. Med. 52: 923–929, 1960.
60. Freeman, L., Engelberg, H. and Dudley, A.: Plasma heparin levels. I. A method for determination of plasma heparin based on anticoagulant activity. Amer. J. clin. Path. 24: 599–606, 1954.
61. Frohn, H., Haanen, C. and Morselt, G.: Thrombotest. Lancet 2: 553, 1960.
62. Fuller, J. A.: Experiences with long-term anticoagulant treatment. Lancet 2: 489–492, 1959.
63. Ghanem, M. H.: Rectal and sublingual heparin. Lancet 2: 907, 1958.
64. Giacomazzi, G.: Influence de l'héparine sur la fibrinolyse activée par la streptokinase. Sang 29: 614–619, 1958.
65. Gilchrist, A. R.: Problems in management of acute myocardial infarction. Brit. med. J. 1: 215–219, 1960.
65a. Gillam, P. M. S.: Prognosis and prophylaxis after coronary occlusion. Lancet 2: 1142–1143, 1960.
66. Gillman, T. and Naidoo, S. S.: *In vitro* effects of heparin and calcium ions on lipæmic serum. Nature, Lond. 179: 904–905, 1957.
67. Godlowski, Z. Z.: Prevention of hormonal eosinopenia and lymphopenia by inhibition of clotting in blood: preliminary report. Brit. med. J. 1: 854–855, 1951.
68. Gordon, R. R. and Dean, T.: Foetal deaths from antenatal anticoagulant therapy. Brit. med. J. 2: 719–721, 1955.
69. Gori, E.: The antibacterial activity of coumarin and indanedione compounds. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 271–274. Schwabe, Basel, 1955.
70. Greene, R.: Management of acute myocardial infarction. Brit. med. J. 1: 497, 1960.
71. Greig, H. B. W.: Christmas-factor (factor IX) deficiency produced by concurrent administration of heparin with coumarin drugs. Lancet 2: 25–26, 1959.
72. Greig, H. B. W. and Tattersall, J. C.: Evidence for the existence of a third serum clotting factor. Brit. J. Haemat. 2: 421–429, 1956.
73. Griffiths, F. E. D.: Ethyl biscoumacetate as inhibitor of sickling. Lancet 2: 20–21, 1955.
73a. Groth, O. and Tengström, B.: Haemorrhagic necrosis of the skin during dicoumarol therapy. Acta derm.-venereol., Stockh. 40: 104–107, 1960.
74. Guthaner, E.: Sensitivity to phenindione. Brit. med. J. 1: 202–203, 1960.
75. Hadfield, G.: Thrombosis. Ann. roy. Coll. Surg. 6: 219–234, 1950.
76. Hahn, P. F.: Abolishment of alimentary lipaemia following injection of heparin. Science 98: 19–20, 1943.
77. Harding, D.: Effect of heparin on artificial activation in the frog egg. Proc. Soc. exp. Biol., N. Y. 71: 14–15, 1949.
78. Hardisty, R. M.: The reaction of blood coagulation factors with brain extract. Brit. J. Haemat. 1: 323–332, 1955.
79. Hartmann, R. C., Meng, H. C. and Thorne, C. B.: Lipaemia-clearing and anticoagulant effects of small amounts of heparin. J. appl. Physiol. 7: 549–552, 1955.
80. Hicks, N. D. and Bonnin, J. A.: The behaviour of coagulation factors during anticoagulant therapy with special reference to the one-stage test as an index of therapy. Brit. J. Haemat. 5: 194–202, 1959.
81. Hjort, P. and Stormorken, H.: A study of the in vitro and in vivo effects of a synthetic heparin-like anticoagulant: dextran sulphate. Scand. J. clin. Lab. Invest. 9: suppl. 29, 1957.

82. Hobson, F. C. G. and Witts, L. J.: A venom-lecithin reagent for the accelerated clotting test (prothrombin time). J. Path. Bact. 52: 367–381, 1941.
83. Honey, G. E. and Truelove, S. C.: Prognostic factors in myocardial infarction. Lancet 1: 1155–1161, 1209–1212, 1957.
84. Honey, G. E. and Truelove, S. C.: Long-term anticoagulant therapy. Lancet 1: 1299, 1959.
84a. Huggins, C. E.: Blood vessel thromboplastins and early thrombosis after vascular operations. Surgery 48: 724–732, 1960.
84b. Hugues, J.: Thrombose et hémostase spontanée. A film made in the Institut de Clinique et de Pathologie médicales, Université de Liège. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, p. 386, Schwabe, Basel, 1955.
85. Hunt, J. H. C.: Sensitivity to phenindione. Brit. med. J. 1: 202, 1960.
86. Hunter, R. B. and Walker, W.: Neodymium 3-sulpho-isonicotinate and blood coagulation. Brit. med. J. 2: 1214–1216, 1956.
87. Hunter, W. C., Krygier, J. J., Kennedy, J. C. and Sneeden, V. D.: Etiology and prevention of thrombosis in deep leg veins. Surgery 17: 178–190, 1945.
88. Ingram, G. I. C.: Observations in a case of multiple haemostatic defect. Brit. J. Haemat. 2: 180–193, 1956.
89. Ingram, G. I. C. and Armitage, P.: The effect of penicillin and of streptomycin on blood coagulation in normal subjects. J. Pharm., Lond. 4: 1047–1061, 1952.
90. Ingram, G. I. C. and Armitage, P.: The "normal range" of the prothrombin time estimated by Quick's method. J. clin. Path. 12: 91–92, 1959.
91. Ingram, G. I. C. and Forwell, G. D.: The anticoagulant activity of dextran sulphate—II. The effect of dextran sulphate on the one-stage prothrombin time. J. Pharm., Lond. 8: 589–601, 1956.
92. Ingram, G. I. C., Norris, P. R. and Tanner, E. I.: Acute coagulation disorders at parturition. J. Obstet. Gynæc., Brit. Emp. 67: 367–383, 1960.
93. Jaques, L. B.: Dicoumarol drugs and the problem of hæmorrhage. Canad. med. Ass. J. 81: 848–854, 1959.
94. Jaques, L. B. and Charles, A. F.: The assay of heparin. Quart. J. Pharm. 14: 1–15, 1941.
95. Jaques, L. B. and Dunlop, A. P.: The effect of calcium concentration on the prothrombin time of dogs treated with dicoumarol. Amer. J. Physiol. 143: 355–360, 1945.
96. Jaques, L. B. and Ricker, A. G.: The relationship between heparin dosage and clotting-time. Blood 3: 1197–1212, 1948.
97. Jeavons, S. M. and Ricketts, C. R.: The effect of dextran sulphate injections on serum lipoproteins. J. clin. Path. 9: 255–256, 1956.
98. Jenkins, J. S.: The thromboplastic activity of Russell's Viper venom and its relationship to factor VII. J. clin. Path. 7: 287–289, 1954.
99. Jewell, P., Pilkington, T. and Robinson, B.: Heparin and ethyl biscoumacetate in prevention of experimental venous thrombosis. Brit. med. J. 1: 1013–1016, 1954.
100. Jones, N. L.: Hepatitis due to phenindione sensitivity. Brit. med. J. 2: 504–506, 1960.
101. Jorpes, J. E.: Heparin in the treatment of thrombosis, pp. 163–164. Oxford University Press, 1946.
102. Jorpes, J. E.: Bibliography of Karl Paul Link. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 175–178. Schwabe, Basel, 1955.
103. Jubelirer, R. A. and Glueck, H. I.: Capillary fragility studies (Göthlin test) on one hundred patients receiving dicumarol. J. Lab. clin. Med. 34: 448–457, 1949.
104. Juel-Jensen, B. E.: Sensitivity to phenindione: report of a case of severe diarrhoea. Brit. med. J. 2: 173–174, 1959.
105. Jürgens, R. and Studer, A.: Zur antagonistischen Wirkung von Vitamin K_1 gegenüber Dicumarol-Analogen. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 341–346. Schwabe, Basel, 1955.
106. Kellaway, G.: Clinical evaluation of "Miradon." Brit. med. J. 2: 889–891, 1958.
107. Keyser, J. W. and Payne, R. B.: A simplification in the estimation of "prothrombin time" for the control of anticoagulant therapy. J. clin. Path. 13: 102–104, 1960.
108. Kimura, E. T., Young, P. R., Stein, R. J. and Richards, R. K.: Some pharmacologic characteristics of hexadimethrine bromide (polybrene)—a new antiheparin agent. Tox. appl. Pharmacol. 1: 185–202, 1959.
109. Koller, F.: Le facteur X. Rev. Hémat. 10: 362–367, 1955.
110. Korst, D. R. and Kratochvil, C. H.: "Cryofibrinogen" in a case of lung neoplasm associated with thrombophlebitis migrans. Blood 10: 945–953, 1955.
111. Lange, K. and Loewe, L.: Subcutaneous heparin in the Pitkin menstruum for the treatment of experimental human frost bite. Surg. Gynec. Obstet. 82: 256–260, 1946.
112. Lehmann, J.: Hypoprothrombinæmia produced by methylene-bis-(hydroxycoumarin): its use in thrombosis. Lancet 1: 318, 1942.
113. Lempert, H. and Poller, L.: Christmas factor in Thrombotest. Lancet 1: 63, 1960.
113a. Lempert, H. and Poller, L.: Evaluation of thrombotest in the control of anticoagulant therapy. Lancet 2: 1115–1119, 1960.
114. Leroy, G. V., Halpern, B. and Dolkert, R. E.: An indirect, quantitative method for the estimation of heparin activity in vitro: the heparin-protamine titration test. J. Lab. clin. Med. 35: 446–458, 1950.
115. Loomis, T. A.: Antithrombin and heparin in human blood. J. Lab. clin. Med. 34: 631–636, 1949.
116. Loughridge, W. M.: Long-term anticoagulant treatment of coronary thrombosis in general practice. Brit. med. J. 2: 217–220, 1959.
117. Lovell, R.: Corticosteroid purpura. Lancet 1: 548, 1960.

118. McMichael, J.: Long-term anticoagulant treatment for coronary-artery disease. Lancet 1: 528, 1958.
119. McMichael, J.: Long-term anticoagulant therapy. Brit. med. J. 1: 970, 1959.
119a. McMichael, J. and Parry, E. H. O.: Prognosis and anticoagulant prophylaxis after coronary occlusion. Lancet 2: 991–998, 1960.
120. MacMillan, R. L. and Brown, K. W. G.: Heparin and thromboplastin. J. Lab. clin. Med. 44: 378–386, 1954.
121. MacMillan, R. L., Brown, K. W. G. and Watt, D. L.: Prothrombin time of capillary blood for outpatient anticoagulant therapy. Amer. J. med. Sci. 238: 443–447, 1959.
121a. MacMillan, R. L., Brown, K. W. G. and Watt, D. L.: Long-term anticoagulant therapy after myocardial infarction. J. Canad. med. Ass. 83: 567–570, 1960.
122. Macpherson, A. I. S.: Treatment of hæmorrhagic disease of the newborn. Brit. med. J. 2: 433–436, 1941.
123. Manchester, B.: The value of continuous (1 to 10 years) long-term anticoagulant therapy. Ann. intern. Med. 47: 1202–1209, 1957.
124. Manchester, B. and Rabkin, B.: The control of dicumarol therapy in myocardial infarction by a simple blood prothrombin test. Circulation 10: 691–698, 1954.
125. Mann, F. D., Mann, J. D. and Bollman, J. L.: The coagulation defect of vitamin K deficiency compared with that caused by dicumarol. J. Lab. clin. Med. 36: 234–237, 1950.
126. Marks, J., Truscott, B. M. and Withycombe, J. F. R.: Treatment of venous thrombosis with anticoagulants: review of 1135 cases. Lancet 2: 787–791, 1954.
126a. Marshall, J. and Shaw, D. A.: Anticoagulant therapy in acute cerebrovascular accidents: a controlled trial. Lancet 2: 995–998, 1960.
127. Mather, G. and Riley, C.: Idiosyncrasy to phenindione. Brit. med. J. 2: 506–507, 1960.
128. Matthews, H. L., Meynell, M. J., Parsons, C. G., Warburton, E. G. and Waterhouse, J. A. H.: Prothrombin pattern over the 24 hours in patients receiving oral anticoagulants. Brit. med. J. 2: 947–948, 1955.
129. Matthews, J. M. and Walker, W.: Control of anticoagulant therapy: a trial of Thrombotest. Lancet 2: 1159–1163, 1959.
130. Mawson, C. A.: The use of Russell Viper venom and lecithin as thromboplastin in the estimation of prothrombin. J. Lab. clin. Med. 34: 458–472, 1949.
131. Mayer, P. M., Dreyfus, C. G. and Bugnard, C.: Les thromboses intravasculaires dans le syndrome d'hémorragie par défibrination. Gynæcologia (Basel) 138: 87–103, 1954.
132. Merskey, C. and Lackner, H.: The coagulability of blood in relation to coronary heart disease. Post Grad. med. J. 35: 203–207, 222, 1959.
133. Merskey, C., Sapeika, N., Uys, C. J. and Bronte-Stewart, B.: Experimentally-induced atheroma in rabbits: effect of an anticoagulant drug (phenindione) on its development. S. Afr. J. Lab. clin. Med. 5: 248–255, 1959.
134. Meyer, O. O.: Use of anticoagulants in the treatment of coronary artery disease. Postgrad. Med. 24: 110–117, 1958.
135. Meyer, O. O. and Howard, B.: Production of hypoprothrombinemia and hypocoagulability of the blood with salicylate. Proc. Soc. exp. Biol., N. Y. 53: 234–237, 1943.
136. Mickerson, J. N.: Hæmorrhage during phenindione therapy. Brit. med. J. 1: 1522–1523, 1958.
137. Millar, G. J., Mersereau, M. O., Lowenthal, J. and Jaques, L. B.: Distribution of phenylindanedione in blood and tissues after oral and intravenous administration. Thromb. Diath. Hæm. 2: 236–249, 1958.
138. Mitchell, J. R. A.: Inhibition of heparin clearing by platelets. Lancet 1: 169–172, 1959.
139. Mitchell, J. R. A. and Bronte-Stewart, B.: Alimentary lipæmia and heparin clearing in ischæmic heart-disease. Lancet 1: 167–169, 1959.
139a. Morgan, A. D.: The Pathogenesis of Coronary Occlusion, chap. 22, Charles C Thomas, Springfield, Ill., 1956.
140. Moser, K. M.: Intravenous administration of fibrinolysin: its systemic toxicity and effect upon components of the coagulation mechanism. Angiology 10: 253–258, 1959.
141. Muldowney, F. P. and Banks, P.: Kaluretic effect of heparin. Lancet 1: 548–549, 1960.
142. Murray, D. W. G., Jaques, L. B., Perret, T. S. and Best, C. H.: Heparin and thrombosis of veins following injury. Surgery 2: 163–187, 1937.
143. Nichol, E. S. and Fassett, D. W.: Attempt to forestall acute coronary thrombosis; preliminary note on continuous use of dicumarol. Sth. med. J. (Bgham, Ala.) 40: 631–637, 1947.
143a. Nichol, E. S., Keyes, J. N., Borg, J. F., Coogan, T. J., Boehrer, J. J., Mullins, W. L., Scott, T., Page, R., Griffith, G. C. and Massie, E.: Long-term anticoagulant therapy in coronary atherosclerosis. Amer. Heart J. 55: 142–152, 1958.
144. Nour-Eldin, F.: Christmas factor in Thrombotest. Lancet 2: 913, 1959.
145. Nour-Eldin, F.: Christmas factor in Thrombotest. Lancet 2: 1091–1092, 1959.
146. O'Brien, J. R.: The effect of heparin on the early stages of blood coagulation. J. clin. Path. 13: 93–98, 1960.
147. Oliver, M. F. and Boyd, G. S.: The clearing by heparin of alimentary lipæmia in coronary artery disease. Clin. Sci. 12: 293–298, 1953.
148. Olwin, J. H. and Koppel, J. L.: Practical aspects of long-term anticoagulant therapy. Arch. intern. Med. 100: 842–847, 1957.
149. Owren, P. A.: Long-term dicumarol treatment in cardiovascular disease—technique and results. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 1085–1094. Schwabe, Basel, 1955.
150. Owren, P. A.: Thrombotest: a new method for controlling anticoagulant therapy. Lancet 2: 754–758, 1959.
151. Owren, P. A.: Selection of patients for life-long anticoagulant therapy. Sært. Farm. 15: 73–84, 1959.
152. Owren, P. A.: The laboratory control of anticoagulant therapy in large groups of patients. Sært. Farm. 15: 92–102, 1959.

153. Owren, P. A.: Christmas factor in Thrombotest. Lancet 1: 436, 1960.
154. Owren, P. A.: Control of anticoagulant therapy. Lancet 1: 600, 1960.
154a. Owren, P. A.: Thrombotest. Lancet 2: 931, 1960.
155. Owren, P. A. and Aas, K.: The control of dicumarol therapy and the quantitative determination of prothrombin and proconvertin. Scand. J. clin. Lab. Invest. 3: 201–208, 1951.
156. Palmer, H., Sommerfelt, S. C. and Berg, R.: Some practical experiences with Thrombotest. Sært. Farm. 15: 103–109, 1959.
157. Parker, R. L. and Barker, N. W.: Effect of anticoagulants on the incidence of thromboembolic complications in acute myocardial infarction. Proc. Mayo Clin. 23: 367–378, 1948.
158. Parkin, T. W. and Kvale, W. F.: Neutralisation of the anticoagulant effects of heparin with protamine (salamine). Amer. Heart J. 37: 333–342, 1949.
159. Paul, H. A., Abscott, P. M., Koppel, J. L. and Olwin, J. H.: Clinical experience with the anticoagulant anisindione (Miradon). Surg. Gynec. Obstet. 108: 605–615, 1959.
160. Payne, R. W.: Side-effects of phenindione. Brit. med. J. 2: 667, 1960.
161. Peyman, M. A.: The value of a chemical test for the detection of blood in the urine during anticoagulant therapy. Lancet 2: 496–497, 1956.
162. Peyman, M. A.: The significance of hæmorrhage during the treatment of patients with the coumarin anticoagulants. Acta med. scand. 162: suppl. 339, 1958.
162a. Poole, J. C. F.: A study of artificial thrombi produced by a modification of Chandler's method. Quart. J. exp. Physiol. 44: 377–384, 1959.
163. Portmann, A. F. and Holden, W. D.: Protamine (Salamine) sulphate, heparin and blood coagulation. J. clin. Invest. 28: 1451–1458, 1949.
164. Powell, D. E. B.: A comparison of brain thromboplastin preparations used for testing prothrombin efficiency. J. clin. Path. 10: 262–266, 1957.
165. Quick, A. J.: The development and use of the prothrombin tests. Circulation 19: 92–96, 1959.
166. Quick, A. J.: Intravascular clotting. Lancet 1: 774–775, 1960.
167. Quick, A. J., Shanberge, J. N. and Stefanini, M.: The effect of heparin on platelets in vivo. J. Lab. clin. Med. 33: 1424–1430, 1948.
168. Quick, A. J., Stanley-Brown, M. and Bancroft, F. W.: A study of the coagulation defect in hemophilia and in jaundice. Amer. J. med. Sci. 190: 501–511, 1935.
169. Quick, A. J. and Stefanini, M.: Experimentally induced changes in the prothrombin level of the blood. J. biol. Chem. 175: 945–952, 1948.
170. Quick, A. J. and Stefanini, M.: Effect of dicoumarol on concentration of the labile factor. Proc. Soc. exp. Biol., N. Y. 72: 232–234, 1949.
171. Rapaport, S. I. and Ames, S. B.: Clotting factor assays on plasma from patients receiving intramuscular or subcutaneous heparin. Amer. J. med. Sci. 234: 678–686, 1957.
172. Robinson, D. S. and French, J. E.: The role of albumin in the interaction of chyle and plasma in the rat. Quart. J. exp. Physiol. 38: 233–239, 1953.
172a. Robinson, D. S. and French, J. E.: Heparin, the clearing factor lipase, and fat transport. Pharmacol. Rev. 12: 241–263, 1960.
173. Rodman, T., Ryan, C. S. and Pastor, B. H.: A comparative study of four prothrombinopenic anticoagulant drugs. Amer. J. Med. 27: 411–423, 1959.
174. Roseman, S. and Green, H.: A colorimetric method for the determination of dicoumarol (3,3'-methylene bis(4-hydroxycoumarin)) in plasma. J. Lab. clin. Med. 37: 321–324, 1951.
175. Roskam, J.: Arrest of Bleeding. Charles C Thomas, Springfield, Ill., 1954.
176. Roth, K. L.: Interaction of heparin with auto-agglutinins in idiopathic acquired hemolytic anemia. Proc. Soc. exp. Biol., N. Y. 86: 352–356, 1954.
177. Roth, K. L. and Frumin, A. M.: Effect of intramuscular heparin on antibodies in idiopathic acquired hemolytic anemia. Amer. J. Med. 20: 968–970, 1956.
178. Rothnie, N. G. and Kinmonth, J. B.: Bleeding after perfusion for open heart surgery. Brit. med. J. 1: 73–78, 1960.
178a. Rothnie, N. G. and Kinmonth, J. B.: The neutralisation of heparin after perfusion. Brit. med. J. 2: 1194–1197, 1960.
179. Russek, H. I. and Zohman, B. L.: Limited use of anticoagulants in acute myocardial infarction: analysis of one thousand "good risk" cases. J. Amer. med. Ass. 163: 922–926, 1957.
180. Samuels, P. B. and Webster, D. R.: Role of venous endothelium in inception of thrombosis. Ann. Surg. 136: 422–438, 1952.
181. Sawyer, P. N., Deutsch, B. and Pate, J. W.: The relationship of bio-electric phenomena and small electric currents to intravascular thrombosis. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 415–421. Schwabe, Basel, 1955.
182. Scarborough, H. and Shuster, S.: Corticosteroid purpura. Lancet 1: 93–94, 1960.
183. Schlatmann, R. J. A. F. M., Prenen, H., Jansen, A. P. and Majoor, C. L. H.: The natriuretic action of heparin and some related substances. Lancet 1: 314–317, 1960.
184. Schlatmann, R. J. A. F. M., Prenen, H., Jansen, A. P. and Majoor, C. L. H.: Effect of heparin and Rol-8307 on kaluresis. Lancet 1: 880, 1960.
185. Schmid, J. and Stockinger, L., 1951. *See:* Wright, Kubik and Hayden (249).
186. Schneider, C. L.: Fibrin embolism (disseminated intravascular coagulation) with defibrination as one of end results during placentæ abruptio. Surg. Gynec. Obstet. 92: 27–34, 1951.

187. SEVITT, S.: Ætiology and pathogenesis of deep vein thrombosis. Lancet 1: 384–385, 1960.
188. SEVITT, S. AND GALLAGHER, N. G.: Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. Lancet 2: 981–989, 1959.
189. SHAPIRO, S.: Warfarin sodium derivative (coumadin sodium). An intravenous hypoprothrombinemia-inducing agent. Angiology 4: 380–390, 1953.
190. SHAPIRO, S. AND WEINER, M.: Coagulation, Thrombosis and Dicumarol, pp. 25–27. Brooklyn Medical Press, New York, 1949.
191. SHEPHERD, D. M., WALKER, W. AND HUNTER, R. B.: Coumarin anticoagulant drugs: chemistry and mode of action. Mfg Chem. 25: 5–9, 1954.
192. SHIONOYA, T.: Studies in experimental extracorporeal thrombosis. II. Thrombus formation in normal blood in the extracorporeal vascular loop. J. exp. Med. 46: 13–17, 1927.
Studies in experimental extracorporeal thrombosis. III. Effects of certain anticoagulants (heparin and hirudin) on extracorporeal thrombosis and on the mechanism of thrombus formation. J. exp. Med. 46: 19–26, 1927.
Studies on experimental extracorporeal thrombosis. IV. Effects of certain physical and mechanical factors on extracorporeal thrombosis with and without the use of anticoagulants. J. exp. Med. 46: 957–961, 1927.
Studies in experimental extracorporeal thrombosis. V. Influence of certain chemical substances on extracorporeal thrombosis with special reference to the efficacy of a combination of heparin and magnesium sulfate. J. exp. Med. 46: 963–977, 1927.
193. SHORE, B., NICHOLS, A. V. AND FREEMAN, N. K.: Evidence for lipolytic action by human plasma obtained after intravenous administration of heparin. Proc. soc. exp. Biol., N. Y. 83: 216–220, 1953.
194. SIBLEY, W. A., MORLEDGE, J. H. AND LAPHAM, L. W.: Experimental cerebral infarction: the effect of dicoumarol. Amer. J. med. Sci. 234: 663–677, 1957.
195. SIRAK, H. D., MCCLEERY, R. S. AND ARTZ, C. P.: The effect of coronamide with heparin on the coagulation of the blood. Surgery 24: 811–818, 1948.
196. SISE, H. S., LAVELLE, S. M., ADAMIS, D. AND BECKER, R.: Relation of hemorrhage and thrombosis to prothrombin during treatment with coumarin-type anticoagulants. New Engl. J. Med. 259: 266–271, 1958.
197. SLÄTIS, P.: The synthesis of prothrombin and proconvertin in the reticulo-endothelial system: an experimental study on rats. Scand. J. clin. Lab. Invest. 10: suppl. 33, 1958.
198. SMITH, R. T.: A heparin-precipitable fraction of human plasma. II. Occurrence and significance of the fraction in normal individuals and in various disease states. J. clin. Invest. 36: 605–616, 1957.
199. SMITH, R. T. AND VON KORFF, R. W.: A heparin-precipitable fraction of human plasma. I. Isolation and characterization of the fraction. J. clin. Invest. 36: 594–604, 1957.
200. SOUGIN-MIBASHAN, R. AND HORWITZ, M.: The uricosuric action of ethyl biscoumacetate. Lancet 1: 1191–1197, 1955.
201. SOULIER, J. P.: Le test de tolérance à l'héparine dans le contrôle des traitements anticoagulants par la dicoumarine et ses analogues. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 793–798. Schwabe, Basel, 1955.
202. SOULIER, J.-P. AND LE BOLLOCH, A.-G.: Le test de tolérance à l'héparine "in vitro" dans le contrôle du traitement par la dicoumarine. Sang 22: 122–132, 1951.
203. SPOONER, M. AND MEYER, O. O.: The effect of dicoumarol (3,3'-methylenebis [4-hydroxycoumarin]) on platelet adhesiveness. Amer. J. Physiol. 142: 279–283, 1944.
204. STEFANINI, M. AND DAMESHEK, W.: The Hemorrhagic Disorders, p. 263. Grune & Stratton, New York, 1955.
205. STEIN, H. B.: Long-term anticoagulant therapy for coronary-artery disease. Lancet 1: 911–912, 1958.
206. STERNBERGER, L. A.: Dicumarol therapy controlled by the stabilised thrombin method for determination of prothrombin. Blood 4: 1133–1141, 1949.
207. STOKER, S. B.: Heparin and burns. Brit. med. J. 2: 360, 1951.
207a. SUZMAN, M. M., RUSKIN, H. D. AND GOLDBERG, B.: An evaluation of the effect of continuous long-term anticoagulant therapy on the prognosis of myocardial infarction: a report of 82 cases. Circulation 12: 338–352, 1955.
208. SWANK, R. L.: Changes in blood produced by fat meal and by intravenous heparin. Amer. J. Physiol. 164: 798–811, 1951.
209. TASHJIAN, A. H. AND LEDDY, J. P.: Agranulocytosis associated with phenindione. Arch. intern. Med. 105: 121–125, 1960.
210. TAYLOR, J. D., MILLAR, G. J. AND WOOD, R. J.: A comparison of the concentrations of C^{14} in the tissues of pregnant and non-pregnant female rats following the intravenous administration of vitamin K_1-C^{14} and vitamin K_2-C^{14}. Canad. J. Biochem. Physiol. 33: 691–697, 1957.
211. THIES, H.-A.: Die Bedeutung der Art- und Individualspezifität von Cerebralthrombokinasen zur Überwachung der Dicumarine, Cumarine und seltenen Erden. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 822–828. Schwabe, Basel, 1955.
212. THOMAS, L., SMITH, R. T. AND VON KORFF, R. W.: Cold-precipitation by heparin of a protein in rabbit and human plasma. Proc. Soc. exp. Biol., N. Y. 86: 813–818, 1954.
213. THOMPSON, B. A.: A modified Quick's one-stage test for the control of out-patients on anticoagulant therapy. J. clin. Path. 13: 176, 1960.
214. THUERER, G. R. AND ANGEVINE, D. M.: Influence of dicumarol on streptococcic infection in rabbits. A.M.A. Arch. Path. 48: 274–277, 1949.
215. TIBBS, D. J.: Embolectomy in the limb arteries. Post Grad. med. J. 36: 283–290, 1960.
215a. TODD, J. W.: Prognosis and anticoagulant prophylaxis after coronary occlusion. Lancet 2: 1086, 1960.
216. TOOHEY, M.: Anticoagulants in myocardial infarction. Brit. med. J. 1: 252–255, 1958.
217. TOOHEY, M.: Long-term anticoagulant therapy for coronary thrombosis. Brit. med. J. 2: 473–475, 1958.
218. TOOHEY, M.: Clinical experience with warfarin sodium. Brit. med. J. 2: 892–893, 1958.

219. Toohey, M.: Comparison of Quick's, Owren's and Ware's techniques for the control of anticoagulant therapy. J. clin. Path. **11:** 56–61, 1958.
220. Tudhope, G. R., Cohen, H. and Meikle, R. W.: Alopecia following treatment with dextran sulphate and other anticoagulant drugs. Brit. med. J. **1:** 1034–1037, 1958.
221. Tulloch, J. A. and Gilchrist, A. R.: Anticoagulants in treatment of coronary thrombosis. Brit. med. J. **2:** 965–971, 1950.
222. Tulloch, J. A. and Stuart, K. L.: Ethyl biscoumacetate as inhibitor of sickling. Lancet **1:** 107, 1956.
223. Twidle, R. S. H.: Refractory thrombophlebitis migrans in malignant disease. Practitioner **185:** 205–207, 1960.
224. Unger, P. N. and Shapiro, S.: Hyperprothrombinemia induced by vitamin K in human subjects with normal liver function. Blood **3:** 137–146, 1948.
225. Verstraete, M., Clark, P. A. and Wright, I. S.: Evaluation of prothrombin times performed with different thromboplastins. Acta med. scand. **163:** 105–114, 1959.
226. Verstraete, M. and Vermylen, C.: Intérêt du dosage chimique des dérivés de la coumarine en clinique. Rev. Hémat. **14:** 209–215, 1959.
227. Verstraete, M., Vermylen, C. and Vandenbroucke, J.: Measurement of overall coagulability during coumarin treatment with reference to the Quick test. Acta med. scand. **167:** 127–138, 1960.
228. Vorzimer, J. J., Sussman, L. N. and Marder, M. J.: Prolongation of action of heparin. J. Amer. med. Ass. **138:** 747–748, 1948.
229. Waaler, B. A.: The effect of permanent anticoagulant therapy on symptoms and mortality in angina pectoris. Acta med. scand. **157:** 289–306, 1957.
230. Ware, A. G. and Seegers, W. H.: Two-stage procedure for the quantitative determination of prothrombin concentration. Amer. J. clin. Path. **19:** 471–482, 1949.
231. Ware, A. G. and Stragnell, R.: Improved one-stage prothrombin method. Amer. J. clin. Path. **22:** 791–797, 1952.
232. Warner, E. D., Brinkhous, K. M. and Smith, H. P.: A quantitative study in blood coagulation: prothrombin fluctuations under experimental conditions. Amer. J. Physiol. **114:** 667–675, 1936.
233. Watson, W. C.: Lipæmia, heparin and blood viscosity. Lancet **2:** 366–368, 1957.
234. Weiner, M., Brodie, B. B. and Burns, J. J.: A comparative study of hypoprothrombinemic agents: the physiologic disposition and chemical pharmacology of coumarin and indanedione compounds. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 181–193. Schwabe, Basel, 1955.
235. Weiss, W. A., Gilman, J. S., Catenacci, A. J. and Osterberg, A. E.: Heparin neutralisation with polybrene administered intravenously. J. Amer. med. Ass. **166:** 603–607, 1958.
236. Weld, C. B.: Alimentary lipæmia and heparin. Canad. med. Ass. J. **51:** 578, 1944.
237. Weld, C. B.: Lipæmia, blood lipids and heparin. Canad. med. Ass. J. **54:** 71, 1946.
238. Wessler, S. and Connelly, M. T.: Studies in intravascular coagulation. II. A comparison of the effect of dicumarol and heparin in clot formation in isolated venous segments. J. clin. Invest. **32:** 650–654, 1953.
239. Wessler, S., Morris, L. E., Ho, C. and Moran, J.: Studies in intravascular coagulation. IV. The effect of heparin and dicumarol on serum-induced venous thrombosis. Circulation **12:** 553–556, 1955.
240. Wimhöfer, H. and Hartert, J. 1951: Ergebnisse systematischer Vorbeugung und Behandlung der Thromboembolie mit Antikoagulantien. Geburtsh. u. Frauenheilk. **11:** 1059–1067, 1951.
241. Wise, W. D., Loker, F. F. and Brambel, C. E.: Effectiveness of dicumarol prophylaxis against thromboembolic complications. Surg. Gynec. Obstet. **88:** 486–494, 1949.
242. Witte, S. and Schricker, K. T.: Mikroskopische Untersuchungen über die Wirkung des Antikoagulans Marcumar auf die Gefässpermeabilität. Folia haemat., new ser. **2:** 366–376, 1958.
243. Working Party of the Medical Research Council on Anticoagulant Therapy in Coronary Thrombosis: An assessment of long-term anticoagulant administration after cardiac infarction. Brit. med. J. **1:** 803–810, 1959.
244. Working Party of the Medical Research Council on Anticoagulant Therapy in Coronary Thrombosis: Long-term anticoagulant therapy. Brit. med. J. **2:** 239–240, 1959.
245. Wright, H. P.: The adhesiveness of blood platelets in normal subjects with varying concentrations of anticoagulants. J. Path. Bact. **53:** 255–263, 1941.
246. Wright, H. P.: The adhesiveness of blood platelets in rabbits treated with dicoumarol. J. Path. Bact. 57: 382-385, 1945.
247. Wright, H. P.: Factors influencing the recanalisation of experimentally thrombosed blood vessels. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 565–573. Schwabe, Basel, 1955.
248. Wright, H. P. and Hayden, M.: The effect of diet upon the response to oral anticoagulants. J. clin. Path. **8:** 65–68, 1955.
249. Wright, H. P., Kubik, M. M. and Hayden, M.: Recanalization of thrombosed arteries under anticoagulant therapy. Brit. med. J. **1:** 1021–1023, 1953.
250. Wright, I. S.: Comments on the present status of anticoagulants with a report of new studies dealing with marcoumar (3-[1'-phenyl-propyl-]4-hydroxycoumarin), phosphorylated hesperidin and the use of anticoagulant therapy for the treatment of cerebral vascular thrombosis and emboli. Proc. I. int. Conf. Thromb. Embol., Basel, 1954, pp. 694–712. Schwabe, Basel, 1955.
251. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction. J. Amer. med. Ass. **163:** 918–921, 1957.
251a. Wright, I. S.: The use of anti-coagulants in coronary heart disease. Progress and problems: 1960. Circulation **22:** 608–618, 1960.
252. Wright, I. S., Marple, C. D. and Beck, D. F.: Report of the committee for the evaluation of anticoagulants in the treatment of coronary thrombosis with myocardial infarction. (A progress report on the statistical analysis of the first 800 cases studied by this committee.) Amer. Heart J. **36:** 801–815, 1948.