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DETERMINANTS OF THE RESPONSE TO ORAL ANTICOAGULANT DRUGS IN MAN

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I. GENERAL FACTORS

A. Introduction

Occlusion of his vasculature by the formation of needless clots and harmful thrombi has stricken mankind since antiquity (197). For the past 3 decades oral anticoagulant drugs have been prescribed therapeutically and prophylactically in these thromboembolic disorders (93). This therapy has been the subject of thousands of papers and many reviews (1a, 5, 12, 29, 65, 145, 268, 269, 274, 284, 298, 302, 318, 320, 351, 372, 406, 463, 467, 471, 483, 517, 526, 547, 557, 612, 622, 633, 644, 647, 658, 675), two of which appeared in this journal (268, 547). In 1951, Seegers reviewed the effect of various drugs on blood coagulation (547), and in 1961 Ingram reviewed the clinical use of anticoagulants and the laboratory control of their dosage (268). Since 1961 the knowledge of blood coagulation and thrombogenesis, vitamin K action, and the metabolism and genetic control of the oral anticoagulant drugs has expanded greatly, and the unique role of anticoagulants in the growing understanding of drug interactions in man has been recognized. In this critical review we shall examine the determinants of the response to oral anticoagulant drugs in man, and the general and specific factors affecting this mode of therapy.

Oral anticoagulant therapy is a phenomenon of this century based on the premise that interference with hemostasis reduces the morbidity and mortality of thromboembolic disorders (50). It began on the dusty plains of Canada about 1910 when sweet clover was planted because it flourished on poor soil and it substituted for corn in silage (541). In the 1920's a previously undescribed hemorrhagic disorder in cattle was shown to result from the ingestion of spoiled sweet clover hay (540). In the 1930's the cause of the bleeding was traced to a toxic reduction of the prothrombin concentration in the blood (525). In the 1940's the hemorrhagic agent was identified as bishydroxycoumarin, U.S.P. (Dicumarol®), and the synthesis of it and hundreds of congeners was achieved (318). In the 1950's extensive trials in patients showed anticoagulant therapy to be clinically efficacious in certain conditions (675). In the 1960's the pharmacokinetics of the oral anticoagulant drugs was investigated in detail (5, 647), their significant role in the elucidation of drug interactions was defined (77, 387, 566), and genetic control of their metabolism (620) and of their biologic effect in man (435) and rat (478) was discovered. In the 1970's these drugs might emerge as a taboo of therapeutics yet become a totem of pharmacology.

B. Physician and patient

To review the factors affecting anticoagulant therapy, one must understand the rationale of its use in medical practice. The experimental data in laboratory animals supporting the clinical application of anticoagulant drugs are controversial, in part because the methods used to induce thrombosis in the laboratory are so artificial (128, 256). Though valuable in resolving many of the problems of anticoagulant therapy, animal studies have contributed little to the clinical problem of its indications (268, 405). Thus, like other therapy, the use of anti-

coagulants in patients is essentially empirical and based on clinical trials. If the patient has a condition that is reputed to benefit from treatment with anticoagulants, barring medical and personal contraindications, the decision to give these drugs depends on the doctor's estimate of the evidence that a beneficial result will be obtained (269). Since the negative clinical reports and the constant hazard of hemorrhage have discouraged the indiscriminate use of anticoagulants (354), the physician's enthusiasm for this therapy should educe an equal enthusiasm and cooperation from the patient (145, 185), although the physician should not institute therapy on more liberal indications than are justified on a scientific basis nor should the patient believe the treatment is life-saving (62).

Long-term anticoagulant therapy in patients out of the hospital should never be undertaken unless the patient or someone living with him is willing and able to take the responsibility for his care (622). To qualify, patients must have sufficient literacy and visual acuity to read instructions, be intelligent enough to understand the serious nature of the therapy and the necessity for close control and supervision (365), and have demonstrable consistency in keeping appointments and following instructions (546, 622). The many medical contraindications are well documented (268, 465, 587). Most physicians experienced with this method of treatment give their patients detailed verbal and written instructions about the nature of the therapy, the dangers of abnormal bleeding or symptoms of recurring thromboembolism, the times to contact the physician, the danger of relying on memory for the frequency and size of the drug dose, and the value of keeping a daily diary of the amount of drug actually taken (30, 366, 450, 666). Because of its disputable good, its potential harm, and its many complexities for both physician and patient, anticoagulant therapy has been called a brilliant but illogical triumph (268).

C. Blood coagulation

To analyze the determinants of oral anticoagulant therapy, the labyrinthine complexity of the interaction of a dozen or so disparate factors implicated in the coagulation of blood must be comprehended. For over a century blood clotting has been thought to involve enzymatic action (89). By 1847 the final product of the reaction, the fibrin clot, was predicted to exist in the blood as a liquid precursor called fibrinogen (627). This precursor was attacked by the enzyme thrombin, which evolved during the coagulation process and circulated in an inactive form called prothrombin (538). In the presence of calcium a thromboplastic product or thromboplastin converted prothrombin to thrombin (385, 386). While this classical theory of coagulation in 1905 considered the clotting factors to be enzymes circulating in an inactive or zymogen form (385), some earlier investigators believed coagulation was the result of a physical combination or stoichiometric reaction of the constituents (523, 537). Both theories turned out to be true. By 1962, about a dozen separate plasma proteins or clotting factor activities had been discovered: the factors are I, fibrinogen; II, prothrombin; III, thromboplastin or tissue extract; IV, calcium; V, proaccelerin; VII, proconvertin; VIII, antihemophilic factor (AHF); IX, plasma thrombo-

plastin component (PTC) or Christmas factor; X, Stuart-Prower factor; XI, plasma thromboplastin antecedent (PTA); and XII, Hageman factor (270, 672). Factor Ia is noncovalently bonded or urea-soluble fibrin; Ia′ is covalently bonded or urea-insoluble fibrin; XIIIa is the activated form of factor XIII, fibrin-stabilizing factor; and PL is platelet phospholipid (fig. 1).

Two separate pathways lead to the activation of prothrombin (256, 475). In the *intrinsic system* all the factors necessary are present in the circulating blood, whereas in the *extrinsic system* tissue substances not in the bloodstream are required for its initiation (fig. 1). In the intrinsic system the prothrombin-activating principle (blood thromboplastin) is formed within minutes, whereas in the extrinsic system it is formed within seconds because the early reactions are by-passed (506). Both pathways must be intact for normal hemostasis. In 1964 the reaction sequence of these factors in the intrinsic system was proposed in 2 theories for a unified function of clotting factors leading to formation of the fibrin clot (135, 348). Coagulation was initiated with the conversion of factor XII into an activated form (XIIa) by surface contact with something other than intact vascular endothelium, as demonstrated in experiments *in vitro* with a foreign surface or subendothelial collagen (241, 414, 662). This enzyme then acted on another clotting factor (XI) and its substrate to form another active enzyme (XIa); all clotting factors thus interacted in a given order until prothrombin (II) was activated to thrombin (IIa). Thrombin caused the actual coagulation by converting fibrinogen to a noncovalently bonded fibrin polymer (Ia), which was then converted to covalently bonded fibrin (Ia′) by factor XIIIa (208, 332).

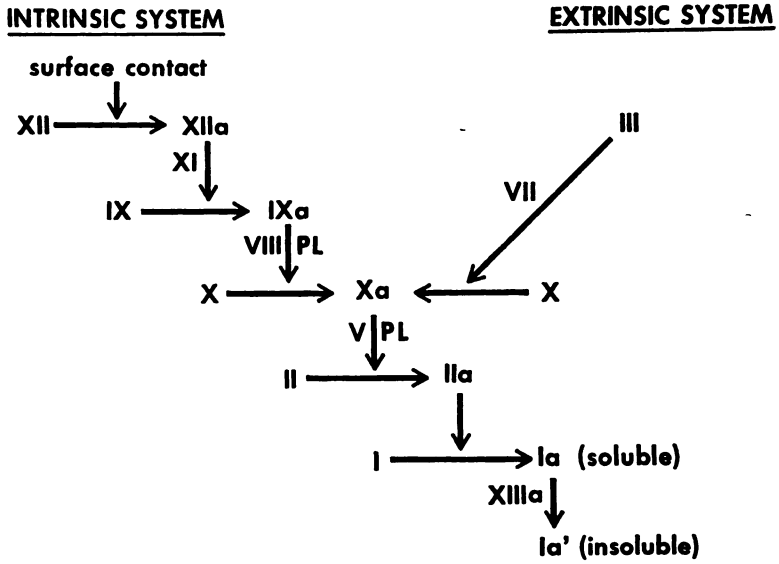

FIG. 1. Reaction sequence for the intrinsic system and the extrinsic system of blood coagulation. Both systems lead to the formation of a urea-insoluble fibrin clot (Ia′). Ionic calcium, which facilitates most of the reactions depicted, has been omitted from the illustration for the sake of clarity. PL is platelet phospholipid.

Since 1964, the sequence theories for prothrombin activation have been tested experimentally to determine whether or not an activated factor with enzyme activity was formed at each step (171). From kinetic data, it was suggested that *prothrombin (factor II) activation* developed from an activation of factor V (76). However, no activated factor V (Va) was formed when a system of purified clotting factors and synthetic substrates was studied (45, 278). Instead, the prothrombin-converting activity was found to develop in a reversible complex formed by activated factor X (Xa), calcium ions, and factor V, which were adsorbed onto a phospholipid surface (44, 455). As factor V could be recovered unchanged from this lipoprotein complex, it was considered to be a cofactor of high molecular weight for Xa (fig. 1) (171). The original sequence theories also suggested that *activated factor IX (IXa)* converted factor VIII to an enzymatic form (135, 348), but VIIIa has not been demonstrated (171a). However, a complex of IXa, VIII, phospholipid, and calcium capable of activating factor X has been demonstrated (258, 536); when the complex was rechromatographed in the absence of calcium, VIII and IXa were recovered unchanged (44). These latter data for the role of complex formation and the absence of activation of factor VIII will be convincing when more purified forms of IXa and VIII become available and when it can be shown that IXa possesses enzymatic activity (171, 241). The contact *activation of factor XII* initiates coagulation and results in a factor (XIIa) that has enzymatic activity (539). Factor XI complexes with XIIa on the surface that may have activated XII (225). This complex, which retains its activity even when removed from the surface, is identical with "activation product" (630) and probably activates factor IX (171). Therefore, it seems likely that factor XIa does not exist as a separate entity. *Factor X* can be activated (Xa) by either the intrinsic or the extrinsic system (349). While the existence of a lipoprotein complex of tissue thromboplastin, factor VII, phospholipid, and calcium ions has been documented, an activated form of factor VII (VIIa) has not been demonstrated (403, 661). Factor VII apparently acts as an obligatory cofactor of high molecular weight for tissue thromboplastin (III) in a lipoprotein complex that activates factor X (171, 312, 404).

The *phospholipids* involved in coagulation are derived from circulating blood platelets, whose "thromboplastic" activity has been correlated with their surface charge (456). They provide a suitable surface for the adsorption and concentration of the circulating clotting factors (588) rather than any specific chemical constituent (240, 278). Because of the adsorption characteristics of the clotting factors involved, it is seemingly possible to demonstrate enzyme-substrate relationships where they in reality may not exist (44). Therefore, reaction sequences for clotting factors cannot be based solely on classic enzyme kinetic analysis (44).

Thus, the coagulation of blood results both from enzymatic and stoichiometric reactions (242) and involves the activation of perhaps 5 zymogens to enzymes (XIIa, IXa, Xa, IIa, and XIIIa) and the formation by physical combination of 3 complexes (171a). In the latter process of complex formation a clotting factor probably acts as a cofactor of high molecular weight for its respective enzyme (XI–XIIa, VIII–IXa, and V–Xa), as factor VII does for tissue thromboplastin

(fig. 1) (171). The complicated and repetitive pattern of coagulation acts as a biologic amplifier in which a several-fold gain of activity is achieved with each stage (348). Some product of coagulation accelerates the development of thrombin and fibrin; hence blood clotting can be termed an autocatalytic reaction (381). It is this chain-reaction pattern and explosive characteristic of blood coagulation that contributes to the growth of a hemostatic plug or the propagation of a thrombus (380). The sequence principle is also applicable to a coagulation theory in which the prothrombin complex is not composed of 4 separate plasma precursors (factors II, VII, IX, and X) but rather these activities are derived from prothrombin alone (349, 548). The physiologic need to link the minute stimulus of contact activation with a final enzymatic explosion of thrombin is mandatory, as a gradual generation of thrombin and slow conversion of fibrinogen to fibrin is hemostatically ineffective (350).

D. Thrombogenesis

To understand the rationale of therapy with oral anticoagulants the factors affecting thrombogenesis must be scrutinized. Past studies on occlusive vascular disease have considered primarily arteriosclerosis of the vessel wall and intravascular coagulation as the main cause of thrombogenesis (382). The resulting methods of treatment by manipulation of dietary lipids and administration of anticoagulant drugs, respectively, have not significantly altered the epidemiology of thromboembolic disorders (545). Thromboembolism continues to be a major public health problem as indicated by the report of the President's Commission on Heart Disease, Cancer, and Stroke (610).

The coagulation of blood has been thought an important factor in arterial disease because complete occlusion of an artery is seldom produced by atheromatous disease alone but also requires formation of a thrombus (301). There is considerable evidence that thrombi are incorporated into vessel wall intima by being overgrown with endothelium to give rise to lesions resembling atherosclerosis (151, 152, 398). While the formation of a blood clot and a thrombus are recognized as being not identical, hemostasis and thrombogenesis seem to be similar processes in that thrombosis is an hemostatic event that occurs intravascularly as a result of a pathologic disturbance of hemostasis (141, 656). In the formation of a white or arterial thrombus the adhesion of circulating platelets to an abnormal vessel wall occurs first, followed by platelet-platelet interaction or aggregation (141, 680). The resultant thrombus develops in the slower areas of rapid blood flow (arteries), and as it grows to occlusive proportions, local stasis occurs, and a red thrombus forms around the white thrombus. At total arterial occlusion a white and red mixed thrombus is present. In contrast, a red or venous thrombus occurs in areas of stagnation or slow blood flow and resembles a blood clot *in vitro*. It consists of a mass of red cells enmeshed in a fibrin network, with the platelets and white cells present in the relatively meager proportions that occur in the circulating blood (383, 680). While platelet aggregates compose the main portion of an arterial thrombus, they also form the "white head" or vessel attachment of the venous thrombus (383). The remainder of a

venous thrombus consists of a long tail of red thrombus, or clot, which easily detaches to form an embolus to the lungs (626). Thus, arterial thrombi act *in situ* by causing local ischemia, whereas venous thrombi cause serious disease by remote embolization.

In all thromboembolic disease the platelet, woefully neglected in past vascular research, is now known to occupy the quintessential position (468). In 1846, a famous triad for thrombogenesis (stasis, hypercoagulability, and vessel wall change) was suggested for the first time, although the consequences of emboli in the pulmonary artery were being discussed (626). In 1851, granular plugs of colorless blood corpuscles and coagulant fibrin were observed in the injured vessels of frogs (659). In 1875, thrombus formation was shown to be the result of massive aggregation and adhesion of the colorless corpuscles to the vascular wall (680). In the 1880's these anuran nucleated cells were correctly identified as blood platelets forming thrombi (61, 155). The aggregating capacity of the granular corpuscles of crustacean hemolymph was first shown in 1880 (204), and in 1927 the corpuscles were found at sites of injury (326). Since these invertebrates (*Limulus polyphemus*) have no clottable protein in their hemolymph, this finding suggested that coagulation and hemocyte aggregation were unrelated (80, 563). Further studies showed that hemocyte aggregation of Crustacea could not be prevented by conditions inhibitory to fibrin formation (112). In 1941, rotation of rabbit blood in a glass flask was shown to result in adherence of platelets to the glass (668). In 1960, passage of whole human blood through a column of glass beads proved to result in adherence of platelets to the glass and to each other (237). The adhesive factor, extracted first from red cells (237), was identified as adenosine diphosphate (ADP) (196). Further studies revealed that platelets contain a high concentration of adenosine triphosphate (ATP), which decreases during aggregation, and since ADP is the first breakdown product of ATP it was suggested that the increased ADP caused adhesiveness of platelets, resulting in the formation of hemostatic plugs physiologically and thromboses pathologically (70). Exposure of platelets to the collagen of vessel walls and damaged tissues causes release of ADP and profound changes in the internal structure of the platelet (261, 682).

Platelet masses formed solely through the action of ADP are unstable (49, 584, 663). After the initial platelet aggregation fibrin becomes an important constituent of a thrombus (79). Production of thrombin is brought about by activation of the intrinsic or extrinsic mechanism of blood coagulation at the site of the platelet mass (357, 397, 408, 662). The thrombin formed not only catalyzes further platelet aggregation by inducing the release of more ADP but also causes fibrin formation which together with the contractile protein of platelets, thrombosthenin (343a), stabilizes the platelet mass (232, 395). A substance (serum thrombotic accelerator) was found in normal mammalian serum that induces thrombosis in areas of vascular stasis (654); at first thought to be a separate entity, it is probably activation product itself (247) or a product of its formation (655).

If the formation of fibrin contributed significantly to an arterial thrombus,

anticoagulant drugs could prevent or reduce their incidence (383). While an arterial thrombus contains mostly platelets and little fibrin, a venous thrombus that embolizes to the lung resembles a blood clot. Anticoagulants have little effect on arterial thrombi clinically (250, 675), in contrast to their significant effect on venous thrombi and pulmonary embolism (42, 552). In acute myocardial infarction the low mortality rate for patients treated with oral anticoagulant drugs has been attributed to the prevention of venous thrombi in the legs and mural thrombi in the heart (383, 505). Thrombosis may occur despite gross defects in the coagulation tests as evidenced by the occurrence of myocardial infarction in patients markedly deficient in factor VIII (67, 69) or factor XII (209, 252) and by the occurrence of massive thromboembolism in patients with marked deficiencies of factor I (268a), factor VII (210), or factor XII (512).

Since the platelet plug forms the bulk of an arterial thrombus, the best therapeutic strategy should be antithrombic agents that interfere with the adherence of platelets to vessel walls and to each other (382, 394, 673a). In 1944, the oral anticoagulants were said to reduce platelet adhesiveness in the rotating flask (586, 669, 670), but this finding could not be confirmed with glass beads (237, 382, 396) except by the originator of the rotating flask technique (251). In 1961, many substances were found to reduce platelet adhesiveness to glass (417). The fact that an enzyme system that removes ADP inhibited the induced aggregation of platelets (232) suggested that ADP forms a "final common path" in platelet aggregation induced by a variety of stimuli (382). Platelet aggregation *in vitro* was not affected by therapeutic levels of either heparin, B.P. (sodium heparin, U.S.P.) or oral anticoagulants except when tested by the rotating tube technique (126), yet it is markedly affected by a variety of compounds whose only common property is vasodilation (382). Adenosine, a competitive antagonist of ADP, inhibits the formation of a white thrombus in the injured cerebral cortical arteries of rabbits (71). The vasodilator dipyridamole (Persantin®) reduces the spontaneous aggregation of platelets in saline (168) and prevents a white thrombus from occurring in injured arteries of the rabbit cerebrum (169) and murine mesentery (143). In 1968, administration of dipyridamole plus oral anticoagulants was shown to decrease the incidence of thromboembolism in patients with prosthetic heart valves (591, 592). Other vasoactive drugs (228, 473) that reduce platelet adhesiveness *in vitro* are aspirin, U.S.P. (418, 653), phenylbutazone, N.F. (Butazolidin®) (397), clofibrate (Atromid-S®) (393), and prostaglandin E_1 (167). The clinical results of agents that inhibit platelet aggregation and thrombus formation in man (673a), particularly for prosthetic heart valves, should augur great interest (11, 159).

E. Vitamin K

The coumarin anticoagulant drugs are believed to function as antimetabolites or antivitamins that compete reversibly with the natural compound vitamin K in the hepatic enzyme system responsible for the synthesis of clotting factors II, VII, IX, and X (374, 500). Factor II is prothrombin itself, while the other 3

factors participate in its conversion to thrombin. These factors are collectively called the prothrombin complex (factors II, VII, and X) or the vitamin K-dependent clotting factors (factors II, VII, IX, and X), and the response to anticoagulant drugs is often called the "prothrombinopenic" or "hypoprothrombinemic" response (613a). The mutual antagonism or allosterism between the drug and the vitamin has been demonstrated in rat liver cell suspension (481), rat liver slices (34, 334, 477, 479), isolated perfused rat liver (343, 420, 594), in intact animals (22, 212, 618), and in man (427, 604). But direct displacement of labeled Dicumarol in the liver of animals or in the blood of man by vitamin K, as a physiologic basis for its antidotal activity (313), could not be confirmed (156, 222, 436, 649). Four basic factors are necessary to prevent avitaminosis K: 1) a normal diet containing the vitamin; 2) the presence of bile of normal composition in the intestine; 3) a normal absorptive surface in the small intestine; and 4) a normal liver (96). Little is known of individual differences in vitamin K metabolism because of the lack of methods sensitive enough to measure physiologic levels of the vitamin in blood or tissue (131, 182).

In 1931, it was shown that chicks fed a diet devoid of ether-soluble components bled and their blood was incoagulable (345). The hemorrhagic syndrome responded only to the restoration of the ether extracts to the diet and the unidentified substance in the extracts was given the name vitamin K (for Koagulations vitamin) (20, 129, 130). The vitamin was isolated and synthesized in 1939 (18, 59, 132). Vitamin K was shown to counteract Dicumarol in animals (442) and man (121, 134, 340, 555). Reduced activity of clotting factors II, VII, IX, and X, but not other clotting factors, results only from vitamin K deficiency or from the administration of oral anticoagulants. The response to vitamin K_1 (phytonadione, U.S.P.) and K_3 (menadione, U.S.P.) may be used to differentiate these 2 conditions (429). The clotting factor defect caused by vitamin K deficiency responds promptly to a small dose of a water-soluble preparation of vitamin K_3 (menadione sodium bisulfite) (3) whereas the clotting defect caused by oral anticoagulants responds poorly to vitamin K_3 and requires large doses of vitamin K_1 for its correction (182, 429). Some investigators have reported that large doses of vitamin K elevate the prothrombin complex above normal levels in animals (180) and man (608), but if the phenomenon occurs it is transient (547).

In 1951, canine studies suggested that vitamin K and coumarin anticoagulants act through a competitive mechanism in which vitamin K participates as the prosthetic group of an enzyme system responsible for the synthesis of the prothrombin complex and the coumarin drug participates as a competitive inhibitor for the enzyme sites in a manner consistent with the law of mass action (16, 500, 502). Subsequent work in rats by 2 different groups did not confirm this theory, as competitive inhibition could not be demonstrated during treatment with a wide range of coumarin doses (35, 336). In man, administration of several therapeutic doses of the anticoagulant sodium warfarin, U.S.P., B.P.A.N. (Coumadin®, Panwarfin®), with 2 dose levels of vitamin K_1 to 6 normal human subjects, showed a mechanism consistent with either allosterism or competition (427).

In 1964, studies with 2 inhibitors of protein synthesis, actinomycin D (421) and puromycin (280), showed that vitamin K can act, respectively, at the transcriptional (messenger RNA) or translational level (ribosome) for synthesis of precursor peptides of the prothrombin complex. Recent work suggested that vitamin K and oral anticoagulants may act competitively at a stage subsequent to peptide synthesis and that their action promotes (vitamin K) or retards (oral anticoagulants) the conversion of the precursor peptides to the 4 vitamin K-dependent clotting factors (34, 245, 246, 594a). Others have suggested that oral anticoagulants act by irreversibly inhibiting the uptake of vitamin K at its site of action; this inhibition can be overcome because with larger doses vitamin K is taken up by an alternate mechanism that is not inhibited by oral anticoagulants (334, 336).

F. The oral anticoagulants

Observations on the pharmacology of oral anticoagulant agents began before they were isolated. In cattle with sweet clover disease the hemorrhagic disorder had a delayed onset of days to weeks and could be transmitted by a pregnant cow to her fetus (526, 541). In 1939, bishydroxycoumarin was identified as the hemorrhagic agent in sweet clover disease of cattle (100). Synthesized coumarin congeners of bishydroxycoumarin (443) as well as noncoumarin compounds with an indanedione nucleus were tested for anticoagulant activity (263) and produced marked hypoprothrombinemic effects in animals and man (57, 58, 289, 376, 582). The effects were completely reversible and resulted in no permanent injury (319, 375, 529). Sodium warfarin (264), the most popular oral anticoagulant in the United States, was initially thought too toxic for man and was recommended as a rodenticide in 1948 (323). In 1951, a man who attempted suicide with repeated large doses of warfarin survived (254). Clinical trials quickly established its safety in man (474, 554), including a President of the United States (323).

The *gastrointestinal absorption* of any drug can be determined only by directly measuring its disappearance from the intestinal tract. As this cannot be done conveniently in man, the assimilation of oral anticoagulants is inferred from their appearance in plasma. Ethyl biscoumacetate, N.F., B.P. (Tromexan®) (87, 206), phenindione, N.N.D., B.P. (Hedulin®, Dindevan®) (544), and warfarin (436, 437) were rapidly and completely absorbed after oral administration, while Dicumarol (206, 437, 651) was slowly and erratically absorbed from the gastrointestinal tract. It was found that the commercially-available tablet form of Dicumarol is poorly absorbed, whereas the powder and solution forms are better absorbed (437). Previous reports on the good absorption of Dicumarol (similar blood levels and hypoprothrombinemic responses with both oral and intravenous forms) were based on experiments with the powdered form (644, 649, 651) which is generally not used commercially (646). With warfarin the form made surprisingly little difference, for warfarin as the free acid was absorbed as rapidly in man as the more water-soluble sodium warfarin (437); warfarin acid tablets (preparation D), when initially exposed to gastric acid, were found to have a dissolution rate as rapid as the sodium warfarin tablets (438).

The *plasma half-life* of anticoagulant drug is rapid for Tromexan, 2 hr (87,

206); intermediate for phenindione, 5 hr (544), acenocoumarin (nicoumalone, B.P.A.N., Sintrom®), 24 hr (64), and warfarin, 44 hr (437); and long for Dicumarol, 1 to 4 days (437), and phenprocoumon, B.P.A.N. (Marcumar®), 6½ days (550). The clotting factor response to warfarin has also been carefully studied in the rat; the half-life for warfarin was 7 hr (483). In man the rate of transformation of unchanged anticoagulant drug was widely divergent for different patients but relatively constant for an individual patient (651). Surprisingly, the half-lives of Tromexan (87, 206) and Dicumarol (206, 437, 651), but not those of warfarin (437) or phenprocoumon (551), were dose-dependent; the smaller doses were metabolized at a faster rate. This curious dose-dependence of the half-life was shown for Dicumarol, in the isolated perfused rat liver, to result from inhibition of its own metabolism with increasing dose levels (400).

The *metabolic products* of the oral anticoagulants are generated by the action of enzymes in the microsomes of liver parenchymal cells (83), and have little hypoprothrombinemic effect (248). In 1952, two metabolic products of Tromexan were identified as tromexan acid and 7-hydroxytromexan (91, 92). With the development in 1962 of a spectrophotometric method for the determination of sodium warfarin concentrations in biologic fluids, a metabolite was detected in human urine that was deduced to be 7-hydroxywarfarin (434). It had been suggested earlier that coumarin anticoagulants were metabolized to salicylic acid (320, 325), but the major pathway of warfarin metabolism in man and rat proved to be hydroxylation by finding in urine 6-hydroxywarfarin, 7-hydroxywarfarin, 8-hydroxywarfarin, 4′-hydroxywarfarin, and a sulfate or glucuronide conjugate of 7-hydroxywarfarin (36, 37, 248, 324). Metabolic products of oral anticoagulants were detected in rat plasma (warfarin) by thin-layer chromatography (265, 315) and by radioactive (Dicumarol and Tromexan) labeling (233), and were identified in rat bile (warfarin) as glucuronide conjugates (476). Metabolic products of Tromexan were also found in bile (91). Apparently, the unchanged anticoagulant drug is transported by the blood to the liver where it is hydroxylated and conjugated by microsomal enzymes (266), excreted into the bile, deconjugated in the intestinal tract, partially resorbed from the intestine into the blood, and then excreted again into the urine as the unconjugated, hydroxylated forms (5, 91 313). Interestingly, the urinary excretion of uric acid in man, rat, and dog is strongly enhanced by the oral anticoagulants (578). The major warfarin metabolite found in stool is 7-hydroxywarfarin (37). A Dicumarol metabolite isolated from the stool of man was deduced from spectrophotometric data to be hydroxy-Dicumarol (437), whereas the Dicumarol metabolite discovered in the urine and stool of rats (106, 107) was said not to be 7-hydroxy-Dicumarol (108). This recent knowledge of the metabolic products of the oral anticoagulants may render the colorimetric and spectrophotometric methods for the determination of Dicumarol (33, 482) and warfarin (156, 201, 317, 434) obsolete, and require a reassessment of oral anticoagulant metabolism in man with more specific methods like chromatography (108, 265, 315, 635). Even a recently developed fluorometric method for the determination of warfarin (114), although it is not affected by many other drugs (431), is not specific for unchanged warfarin (425) because of the marked natural fluorescence of some of the metabolites (427).

The *protein binding* of oral anticoagulants has been extensively studied (87, 424, 425, 439, 649, 651). At therapeutic levels Dicumarol is almost wholly bound (99%) to plasma proteins and plasma albumin fractions; less than 1% of the drug is detected in red blood cells or cerebrospinal fluid (649, 651). Tromexan is less bound (90%) to plasma proteins (87, 649), while warfarin at therapeutic concentrations is 97% bound to human plasma. However, these enumerations of the percentage of drug bound to plasma protein has little meaning even when the concentrations of the drug and protein are stated. Binding data are best presented in physicochemical terms such as the association constant or the free energy change of the interaction. Warfarin has an apparent volume of distribution the size of the albumin space (2½ times the plasma volume) (436). Many nonhypoprothrombinemic effects of oral anticoagulant drugs may be related to protein binding (145, 616). The alleged effect of Dicumarol on blood vessel integrity (402) may have resulted from displacement by the anticoagulant of the highly albumin-bound T-1824 dye used (424). The elevated uptake of triiodothyronine sodium (sodium liothyronine, U.S.P., B.P.; Cytomel®) in the T_3-uptake test (227) *in vitro* was probably a result of the same mechanism. The augmentation of the hypoprothrombinemia of the oral anticoagulants that is produced by phenylbutazone and oxyphenbutazone may result from displacement of the highly albumin-bound coumarin in man (7), whereas the lack of hypoprothrombinemic enhancement in the dog may result from the 5-fold lesser binding of warfarin in the dog (see section II B 2) (426a).

Experiments with continuous flow electrophoresis proved that warfarin was bound only by the albumin fraction of whole human plasma and prompted further study (424). The interaction of the drug and human plasma albumin was then studied by equilibrium dialysis (424). Albumin was found to have 2 strong and several weaker binding sites for warfarin; the free energy of binding was −7.6 kcal/mole at 37°C (425). [It is meaningless to talk about saturation levels of a drug for binding sites on human albumin as no actual plateau has ever been demonstrated for the concentration of bound warfarin, or for any other anion noncovalently bound to albumin, plotted against the concentration of free warfarin (425). Complex formation with anions increases the net negative charge on the albumin molecule and apparently makes more sites available for further binding (424)]. The interaction was exothermic with the evolution of a surprisingly large amount of heat (−3.5 kcal/mole) for an anion-albumin interaction. The magnitude of heat evolution has been confirmed by direct calorimetry (439). The exothermic nature of the binding process and its positive entropy (unavailable energy because of increased molecular disorder) suggest hydrogen bonding and hydrophobic bonding for the binding process.

The binding of sodium warfarin and human plasma was studied further, by equilibrium dialysis, as a function of the pH and of the ionic strength of the supporting medium (425). The warfarin-albumin binding strength rose significantly as the pH was increased from 6.0 to 9.0, while a 20-fold variation of buffer ionic strength caused no significant change in the association constant. Studies of the albumin binding of the urinary metabolites, 6-, 7-, and 8-hydroxywarfarin,

showed a 7- to 23-fold lower binding strength than that of sodium warfarin (425). These data indicate that the molecular basis of the warfarin-albumin interaction is not ionic and that the introduction of the polar hydroxyl groups on the coumarin nucleus by metabolism reduces its hydrophobic binding surface. The marked albumin binding and nonpolar character of warfarin explain the respective presence and absence of the unchanged drug in plasma and urine, while the more polar character and lesser albumin binding of the metabolites probably determine their absence in plasma and presence in urine. The data suggest a direct correlation between the interaction of warfarin and its metabolites with plasma albumin and their interaction with the anticoagulant receptor sites (425).

Correlations of the plasma level of anticoagulant drug and the prothrombin response in man began in 1948 with the development of photometric assays of coumarin drugs in human blood for Tromexan (87, 206, 482), Dicumarol (33, 206, 651), phenindione (544), warfarin (434, 436), and phenprocoumon (550, 551). The therapeutic effect of these drugs is delayed because they act by inhibiting the hepatic production of clotting factors (5); hypoprothrombinemia is not detected until 8 to 12 hr after oral or intravenous administration of the anticoagulant (5, 87, 436, 544, 651). Larger initial doses of anticoagulant hasten the onset of hypoprothrombinemia only up to a certain dose level (for warfarin about ¾ mg drug/kg body weight) beyond which the speed of onset is independent of the dose size (437). Higher blood levels of drug will not result in faster metabolism of the clotting factors already present in the blood (7). The principal effect of the size of the loading dose is on the length of time the drug will remain in the plasma in a concentration above the level required for suppression of production of new clotting factors (7). The longer the drug is above this level, the greater the decrease in clotting factors. No significant difference in the inherent ability of the various oral anticoagulant drugs to produce this maximal rate has been observed (437). When the anticoagulant doses were adjusted to yield the same degree of maximal hypoprothrombinemia, this end point was reached in a shorter time with the more rapidly metabolized drugs, Tromexan, acenocoumarin, and phenindione, than with the slowly metabolized drugs, Dicumarol and phenprocoumon (649). Observations of this type have been misinterpreted as indicating that the rapidly metabolized drugs produce hypoprothrombinemia at a faster rate than the more slowly metabolized drugs. By changing the conditions of this experiment and giving a sufficiently large dose of each drug, similar rates of induction of the hypoprothrombinemic response can be obtained with all the drugs (7, 437). However, the degree and duration of the response varies with the rate of absorption and the metabolic half-life of the anticoagulant drug. Compounds like Tromexan that are absorbed and eliminated rapidly from the blood produce a lesser maximal degree of hypoprothrombinemia and a faster return of the one-stage prothrombin time to normal (7). The erratic plasma levels during long-term therapy with Tromexan correlate well with the marked and unpredictable changes in the one-stage prothrombin time (83). In contrast, long-term use of drugs like warfarin and

Dicumarol that are absorbed and eliminated at slower rates have a longer time to exert their action and hence produce a greater maximum degree of hypoprothrombinemia, a slower return of the one-stage prothrombin time to normal, and a more constant level of hypoprothrombinemia (7).

Attempts to demonstrate significant correlations between plasma drug concentrations and prothrombin complex responses were unsuccessful with Dicumarol because of its prolonged and incomplete absorption (437, 649) and with Tromexan because of its rapid elimination from plasma (482). Furthermore, the dose-dependence of the disappearance rate of both drugs makes interpretation difficult (7). However, in several mammalian species a direct correlation was found between the degree of hypoprothrombinemia and the concentration of Dicumarol found in the liver (274a). Sodium warfarin is more suitable for showing these correlations because its absorption phase is complete and of short duration and its elimination rate is relatively slow and independent of dose (436). In 24 normal persons who received a standard oral dose of 1.5 mg of warfarin/kg body weight, a highly significant correlation was found between the plasma half-life of the drug and the maximal hypoprothrombinemic response and between the plasma concentrations of warfarin at 48, 72, and 96 hr after drug administration and the degree of hypoprothrombinemia observed at these times (7, 436). These relationships have been analyzed by a pharmacokinetic technique in which the rate of synthesis of the prothrombin complex is plotted against the logarithm of the plasma warfarin level (401). A single determination of the warfarin level and the prothrombin response in plasma at 48 hr has been very useful as a screening test for population studies (see section IV B 2) in hereditary resistance to oral anticoagulants (426, 435).

Initiation of therapy with oral anticoagulants usually is accomplished with a large loading dose of the drug followed by progressively smaller doses until a daily maintenance level is reached. The large initial dose is used to produce the greatest anticoagulant effect in the shortest possible time; however, this led to an excessive and dangerous level of anticoagulation in some patients (47). In 1962, it was demonstrated in 3 patients that anticoagulant therapy could be initiated and continued with maintenance doses of warfarin alone (677). In 1968, 3 methods of initiating warfarin therapy were compared in 15 normal subjects. Doses of 1.5 mg of drug/kg body weight, 15 mg of drug/day, and 10 mg of drug/day took 1.1, 2.7, and 5.2 days, respectively, to reach a prothrombin complex activity of less than 35% of normal activity (430). The rates of fall of the 4 vitamin K-dependent clotting factors were compared (see section I G). With the largest anticoagulant dose, only factor VII activity was lower during the first 48 hr, while the activity of factors II, IX, and X fell just as rapidly at all times tested with the 15-mg dose. Therefore, the faster onset of reduction of prothrombin complex activity with the large dose appeared to be entirely the result of the more rapid decline in factor VII activity alone. Since factor VII does not participate in the coagulation phase of thrombogenesis (282) it was suggested that the speed of onset of the antithrombotic effect of oral anticoagulants was the same whether a large loading dose was used or not (430). However,

no statistical study of a clinical series ever has been undertaken on the initiation of oral anticoagulant therapy with and without a large loading dose of the drug.

It was postulated that the loading dose of an oral anticoagulant drug somehow sensitizes the synthesizing mechanism in the liver for the vitamin K-dependent clotting factors so that it becomes more responsive to the subsequent smaller daily doses (649). The effect was said to be over and above that resulting from actual accumulation of the drug in the plasma or liver. This concept of variable sensitivity caused by the oral anticoagulant itself was advanced to explain why a fixed daily dose of drug appears to result initially in the desired level of hypoprothrombinemia, only to lead eventually to either an inadequate or an excessive response (649). We do not accept these theories, because the available data indicate that the principal reasons for difficulty in maintaining a steady state of hypoprothrombinemia are 1) the dose size is really too large or too small and the amount of drug at the hepatic receptor site gradually increases or decreases; 2) the amount of drug available to the receptor site although constant from day to day is actually too much or too little; 3) some factor influences drug metabolism and the amount of drug available to the receptor site becomes higher or lower than that previously found to be sufficient; or 4) some factor other than the oral anticoagulant affects the sensitivity of the hepatic synthesizing mechanism so that a previously satisfactory dose of drug produces a greater or lesser effect than before (7).

G. Laboratory control

To review the parameters of oral anticoagulant therapy the methods of its laboratory control must be examined. This therapy has been controlled primarily by use of the one-stage prothrombin test (504) or one of its modifications (449, 453). The test was designed in 1935 and was based on the classical coagulation theory of 1905 (385): the clotting time is determined in seconds after recalcification of a mixture of oxalated or citrated plasma (the source of prothrombin and fibrinogen) and tissue thromboplastin (504). In isolating bishydroxycoumarin from spoiled sweet clover hay, hemorrhagic concentrates were assayed in rabbits by a one-stage prothrombin time (100, 504). Thus, when the anticoagulant was introduced into clinical medicine in 1941, this test was used for controlling the dosage, and it has remained the standard method of control (50, 268). So important was the assay for the expansion of blood coagulation theory that it has been deemed the most useful coagulation test ever developed (51). Many of the coagulation assays used, such as the partial thromboplastin time and the thromboplastin generation test, are direct outgrowths of the one-stage prothrombin test and are based on the same principle: measurement of the speed of thrombin production as determined by the appearance of a visible fibrin clot (496). Originally the test was thought to measure prothrombin (II) specifically, but it was subsequently found that factors V (447, 492), VII (355, 445), and X (148, 257, 596) were important determinants of the test results. The nonspecific nature of the one-stage prothrombin test was fortunate, because the oral anticoagulants simultaneously depress the activity of 3 factors measured by the test, factors II,

VII, and X (510). In 1952, factor IX was discovered (9, 55) and was found to be vitamin K-dependent and coumarin-sensitive (399, 567); but it is not measurable by the one-stage prothrombin test (568). More specific tests, the two-stage prothrombin determination (639) and the Russell's viper venom-cephalin method (193, 253), were developed but were inadequate for control and were, therefore, dangerous (364, 451, 664).

In the original one-stage prothrombin test it was recognized that a plot of the clotting time in seconds against the activity or concentration of the prothrombin complex yielded a hyperbolic curve (495). The activity in percent of normal was obtained by use of a standard correlation curve prepared by diluting normal plasma with saline and determining the clotting time. Because this technique diluted out the fibrinogen and factor V, the test was modified by using plasma adsorbed with barium sulfate or aluminum hydroxide as a diluent (491). Dilution with adsorbed plasma kept the concentration of fibrinogen and factor V constant since adsorption removes only the coumarin-sensitive factors (II, VII, IX, and X). However, because the resulting hyperbola was so unfavorably shallow or flat, the test system was diluted 10-fold to give a correlation curve even steeper than the original one-stage determination (451). In 1951, the prothrombin and proconvertin (P and P) test, which embodies these modifications, was introduced for the control of anticoagulant therapy (453). Tissue thromboplastin was extracted from human brain rather than rabbit brain, as in the original one-stage method, to increase the test's sensitivity to factor VII and the calcium concentration was kept constant by providing a citrate concentration that was not altered by changes of the patient's hematocrit level (451). The P and P test measured not only prothrombin (II) and proconvertin (VII) but also the coumarin-sensitive factor X, discovered subsequently in 1956 (451).

In 1957, tissue thromboplastin was said to initiate simultaneously both the intrinsic and extrinsic systems of coagulation, and the clotting time was considered to result from the activities of both systems (629). When a weak form of tissue thromboplastin was used, the contribution of the extrinsic system was diminished and the contribution of the intrinsic system, particularly the coumarin-sensitive factor IX, became apparent. In 1959, the thrombotest was introduced to better control anticoagulant therapy; the test employs an all-in-one reagent containing a weak tissue (bovine) thromboplastin to initiate the extrinsic system, the platelet substitute cephalin, adsorbed bovine plasma, and calcium chloride (449). The concentrations of cephalin and thromboplastin were adjusted to accelerate the intrinsic pathway and to decelerate the extrinsic system to reflect more equally the activities of factors II, VII, and X, and particularly factor IX. The thrombotest was soon found to be insensitive to isolated factor IX deficiency (415, 503), but the innovator of the method stated it had been designed to detect severe factor IX deficiency only in the presence of the reduced activities of factors II, VII, and X during anticoagulant therapy (451). This latter claim was refuted by studies showing that factor IX was not depressed more than factors II, VII, or X in long-term anticoagulant therapy (140), even during hemorrhagic episodes (508). The close correlation of the results of the P

and P method and the thrombotest suggested that the latter was not sensitive to factor IX (31). Furthermore, even the complete omission of cephalin from the thrombotest reagent did not significantly alter the clotting time measurement (527). The thrombotest was also criticized because of the higher cost per test, the increased personnel time required because of the long clotting times, the necessity for using siliconized glassware or plastic apparatus, the difficulty of standardizing the test in the individual laboratory, the necessity of doing a simultaneous hematocrit when the capillary blood method was used, and the necessity for siliconized needles and syringes and special citrate solutions when the venous method was used (378, 561). However, others have praised the thrombotest because of the quality control of the human brain thromboplastin used, the reproducibility of the dilution curves, and the excellent clinical results obtained (327a, 507).

Comparative studies of the one-stage prothrombin test, the P and P test, and the thrombotest showed good linear correlations among the 3 tests (31, 595). It was also shown that the one-stage prothrombin test correlated well with the specific assays for factors VII and X (138). The more sensitive thrombotest yielded lower percentages of activity, which resulted in the administration of less anticoagulant drug (527). For example, a thrombotest of 10% activity corresponded to a P and P activity of 17% and a one-stage prothrombin activity of 25% (595). Thus, patients controlled by the thrombotest were under-treated when the dosage was based on the percentage range of the one-stage test, a circumstance that may explain why hemorrhagic episodes occurred less frequently with the thrombotest (31).

Whether anticoagulant therapy was initiated with a large or small loading dose, the activity of the vitamin K-dependent clotting factor with the shortest biologic half-life declined first with the others following accordingly, *i.e.*, VII, IX, X, and II, respectively (430). In 1963, the innovator of the thrombotest found during long-term therapy that factor X was invariably the most depressed factor and factor IX the least depressed and that bleeding because of too large a maintenance dose of anticoagulant was invariably precipitated by factor X deficiency (452). Occasionally, an acute overdosage during long-term therapy resulted in a rapid fall of factor VII because of its very short half-life and bleeding was primarily associated with factor VII depression (452). Apparently, during stable long-term therapy the levels of the vitamin K-dependent clotting factors depend on the production rates of the factors during the partial blockade of their synthesis, which is quite different from their biologic half-lives. The clotting times obtained by both the one-stage prothrombin test and the thrombotest are determined by the vitamin K-dependent clotting factor at the lowest level of activity (244), which in 1968 was found to be factor X for stable long-term anticoagulant therapy, vitamin K deficiency, and chronic liver disease (246). When either factor II or factor VII is much lower than factor X, it becomes rate-limiting (246).

While there can be many causes of bleeding during anticoagulant therapy that are unrelated to the levels of the clotting factor activities, therapy can be

best controlled in most clinical settings by the original one-stage prothrombin test (464). The most important element of the test is the tissue thromboplastin used (495), and each laboratory must determine its own range of safe and hemorrhagic levels (564) for the thromboplastin (24, 54, 472) and technique employed (372). After considerable effort, a reference thromboplastin has been prepared for general use in Great Britain (53, 472). It is hazardous to refer to a one-stage prothrombin test (497) in either seconds or percent of normal activity without indicating the control time, the type of diluent used, and the brand of thromboplastin employed (53, 617). As Dicumarol was first discovered as a hemorrhagic agent in cattle and warfarin is used as a hemorrhagic rodenticide, the primary responsibility of the laboratory consequently should be to prevent these drugs from becoming hemorrhagic poisons in clinical use (52, 683). However, this risk cannot be eliminated entirely, since in many instances bleeding is simply an extension of the therapeutic effect of the anticoagulants (211, 328, 458). Even at a medical center where much attention is given to control the prothrombin time could be maintained within the therapeutic range more than 80% of the time in only 57% of the patients (470). Thus, in light of the laboratory and clinical results obtained the therapeutic feasibility of long-term therapy can legitimately be questioned when one considers the time and effort expended by both patient and physician.

II. INCREASED RESPONSIVENESS: NONHEREDITARY FACTORS

A. Bodily factors that increase the response

1. Vitamin K deficiency. The intake and absorption of vitamin K modifies the response to the oral anticoagulant drugs in man and experimental animals (671). Alfalfa, which contains a high amount of vitamin K, was the only one of the many natural substances tested that could alter the hypoprothrombinemic response to Dicumarol in animals (442). Beginning in 1938, vitamin K deficiency, and presumably increased responsiveness to anticoagulants, has been noted with a wide variety of intestinal diseases: sprue (4, 96), chronic diarrhea (641), intestinal fistula or obstruction (109), ulcerative jejuno-ileitis (572), and ulcerative colitis (109). Vitamin K is abundantly present in these conditions but is prevented from being absorbed (94, 95). Large quantities of mineral oil or activated carbon in the diet (15) produce vitamin K deficiency both clinically (276) and experimentally (39, 166). However, the data to actually document increased responsiveness to oral anticoagulants in these disorders are few, as the intestinal disease that interferes with the absorption of the vitamin also possibly interferes with the absorption of the drugs.

Any disorder that hinders the delivery of bile to the small bowel, such as obstructive jaundice (95, 640) or a biliary fistula (235, 640), reduces the absorption of the fat-soluble vitamin K and results in a reduced prothrombin concentration that can be prevented or relieved by administration of vitamin K (219). By 1941, obstructive jaundice in patients was noted to be analogous, both in the fundamental nature of the bleeding tendency (lack of prothrombin) and in the curative mechanism effected by vitamin K and bile, to the bleeding disease produced

in experimental animals when the drainage of bile to the intestine is prevented by an internal or external biliary fistula. These findings bridged the gap of knowledge between the hemorrhagic syndrome in chicks fed the vitamin K-deficient diet and the bleeding tendency in some jaundiced patients (15). Finally, patients with an external biliary fistula, and particularly those with associated pancreatitis, were shown to be more sensitive to oral anticoagulant drugs (229, 306).

Increased responsiveness to anticoagulant drugs develops during periods of starvation (145, 165, 190). Originally it was believed that the primary physiologic source of vitamin K in man was the synthesis of the vitamin by enteric bacteria in the intestinal tract (21) with relatively little vitamin obtained from dietary intake (17) although cases of nutritional deficiency of vitamin K in man had been reported (3, 78, 291, 598). This belief stemmed from work in 1937, when rats and guinea pigs not only showed no effects from a diet deficient in vitamin K (133) but also continued to excrete the vitamin in the stool (218). It was subsequently shown that the lack of vitamin K deficiency was attributable to ingestion of the vitamin excreted in the feces. When coprophagy was prevented and a vitamin K-free diet administered, vitamin K deficiency quickly developed and the prothrombin time became prolonged (38).

In 10 healthy subjects on a vitamin K-free diet for 3 weeks the mean prothrombin time rose from 14.8 to 16.0 sec. The rise was said to be significant, but the mean control time of the "healthy" subjects was significantly above the normal mean for that laboratory (13.9 sec.) (603). In another study, of 10 patients who were placed on a vitamin K-free regimen for 4 weeks, 7 were also given oral antibiotics (190). The one-stage prothrombin time and the vitamin K-dependent clotting factors remained unchanged in the 3 patients on the vitamin K-free regimen alone but these activities were moderately to markedly reduced in the 7 patients also receiving oral antibiotics. Thus, both dietary deprivation and reduction of intestinal bacteria are necessary to induce vitamin K deficiency in man (26). Curiously, in man vitamin K deficiency occurred in 3 patients on a normal diet and the only clinically detectable cause was *Ascaris* infestation (432, 625). In normal subjects on long-term therapy with oral anticoagulants a vitamin K-free diet markedly prolonged the abnormal prothrombin time and a very high vitamin K diet markedly shortened it almost to normal (498, 603). In 10 patients on long-term anticoagulant therapy large doses of the antibiotic neomycin sulfate, U.S.P. (Mycifradin® sulfate) were given to suppress synthesis of vitamin K by enteric bacteria; little prolongation of the prothrombin time resulted. The investigator interpreted this to mean that relatively little vitamin K came from bacterial synthesis in the intestinal tract (603). When either a vitamin K-free diet or suppression of enteric bacteria is present, the patient gets enough vitamin K to maintain clotting factor activities at near normal levels but not enough to normally counteract the oral anticoagulant, whereas when both are present the response to the same dose of oral anticoagulant is markedly increased. A significant part of the drug dose during routine anticoagulant therapy must necessarily compete with the vitamin K, ingested orally and synthesized intestinally, that is in excess of the minimum daily requirement (190).

2. Hepatic dysfunction. Liver disease potentiates the action of anticoagulant

drugs. In 1905, the experimental production with chloroform of hepatic necrosis in animals was shown to severely affect blood coagulation (146). Subsequent studies showed that the level of plasma fibrinogen decreases (187, 660). In 1937, it was shown in dogs that chloroform-induced hepatic necrosis is associated with a marked reduction in prothrombin concentration, and when small repeated doses of chloroform are given the fibrinogen level remains within normal limits while the prothrombin level falls markedly and hemorrhage often occurs (569, 639). Even chloroform anesthesia for surgery can cause a marked reduction in prothrombin that lasts for days (124), which may be the basis of the "postoperative dip" of prothrombin activity in patients on oral anticoagulants (299). Intact liver function was soon recognized as one of the factors essential to the prevention of avitaminosis K and consequent prothrombin deficiency (95, 681). By 1947, Dicumarol was being administered with caution to patients with nutritional deficiencies or hepatic diseases associated with potential or actual prothrombin deficiency because of the increased incidence of hemorrhage in these patients (14, 516). Patients with congestive heart failure were noted to have an increased responsiveness to oral anticoagulants as hepatic congestion developed (294, 448), and the responsiveness decreased on relief of the congestion by corrective cardiac surgery (590). Development of acute viral hepatitis or intoxication with small doses of carbon tetrachloride in patients on oral anticoagulant therapy resulted in potentiation of the drug action with marked prolongation of the prothrombin time and occurrence of hemorrhagic phenomena (297, 344). In 1959, the biologic half-life of Dicumarol was shown to be not significantly prolonged in 6 patients with cirrhosis of the liver. Therefore the enhanced responsiveness to the anticoagulant was not the result of prolonged metabolism of the drug (85) as many had assumed (56). The enhancement was concluded to be the additive result of the anticoagulant and the liver disease on the synthesis of the vitamin K-dependent clotting factors and also the effect of the liver disease on factor V production (559). Administration of vitamin K to patients with damaged livers may not only be ineffective but may also prolong the prothrombin time (583, 609). This ineffectiveness is not surprising, as a remarkable variety of hemostatic defects has been described in patients with liver disease, including abnormalities of platelets, blood vessels, many of the components of blood coagulation (factors I, II, V, VII, IX, and X), and clot stability (158, 511, 585).

In 1961, the responsiveness of 5 patients with mild liver disease to a single oral dose of phenindione, 4 mg/kg body weight, was compared to the effect in 5 normal control subjects. The group with the liver disease had a greater and more prolonged increase in the prothrombin time (559). The same investigators conducted further studies to determine whether or not coumarin anticoagulants had hepatoxic properties; long-term therapy in patients had no effect on the tests used to measure hepatic function. This confirmed earlier observations in animals (322), even when massive doses of the anticoagulant were given (632). Hepatitis with jaundice and fever is an occasional complication of therapy with the indanedione type of oral anticoagulant, but whether the disease is cholestatic or hepatocellular has not been determined (559) even by liver biopsy (461). In 1962, reports of

adverse reactions to the indanedione anticoagulant phenindione in 136 patients were reviewed: a skin rash occurred in 100 patients, fever in 34, diarrhea in 20, granulocytopenia in 18, stomatitis in 14, nephropathy in 5, and jaundice in 10 (462). These reactions have been reported only rarely for the coumarin type of oral anticoagulants.

The liver is thought to be the sole site of production of the vitamin K-dependent clotting factors. In 1947, it was shown that the clotting defect in plasma from Dicumarol-treated rats could be corrected by perfusing the blood through the liver of an untreated rat but not by perfusion through the liver of a Dicumarol-treated rat (343). In 1959, it was shown that the synthesis of clotting factors in isolated rat liver slices *in vitro* was blocked by warfarin and the warfarin effect could be reversed by pretreatment of the donor rat with vitamin K (479). The synthesis of prothrombin in the bovine and human hepatic parenchymal cell was demonstrated by immunofluorescent staining (40, 41). In 1966, the hepatic synthesis of prothrombin was studied in vitamin K-deficient rats treated with vitamin K and inhibitors of protein synthesis; it was concluded that the vitamin K-dependent step occurred after the ribosomal synthesis (see section I E) of protein (34, 280, 334, 420, 594). From kinetic analysis of the clotting factor response to Dicumarol, the occurrence of an inhibitor or an inactive precursor of Factor X in the plasma of both chronically anticoagulated and vitamin K-deficient patients was suggested (243, 245), but the inhibitor or precursor could not be found by adsorption with barium sulfate (333). In 1968, by an immunologic technique for the determination of prothrombin (286), 2 fractions of prothrombin were found in patients treated with Dicumarol (410). The abnormal prothrombin (II) fraction did not form a complex with calcium, was not adsorbable with barium sulfate, was not activated to thrombin (IIa) on recalcification, and was said to consist of probably incomplete prothrombin molecules ("preprothrombin") released from the liver in conditions with relative vitamin K deficiency (200, 285). An immunologic study with a human prothrombin antiserum detected a nonthrombin cleavage product during prothrombin activation (558). Further supporting data are needed to verify the following speculations: 1) that a complex of prothrombin and calcium might be the only form of prothrombin capable of being activated (199); and 2) that the close correlation between the concentration of immunologically normal prothrombin and the activity of factors II, VII, and X, as determined by the P and P test, suggests that factors VII and X are not unique proteins (548) but derivatives of prothrombin (391).

3. Hypermetabolism. Hypermetabolic states result in increased responsiveness to oral anticoagulant drugs. In 1943, it was shown that induction of fever in rats augmented the response to Dicumarol (519). In 1955, the clotting time of whole blood was found to be prolonged in hyperthyroid states (214). Dicumarol and thyroxine (sodium levothyroxine, U.S.P.) both decreased the oxidative phosphorylation of mitochrondria *in vitro*, and this inhibitory activity closely correlated with the anticoagulant effect of Dicumarol (360). Dicumarol also inhibited *in vitro* the activity of the hepatic enzyme DPNH oxidase (335). However, these observations were difficult to correlate with anticoagulant activity in the intact

animal as no alteration in hepatic function or enzymes nor any physiologic changes consistent with an uncoupling of oxidative phosphorylation could be found (221). It was concluded that Dicumarol does not exert its therapeutic effect by dissociating oxidation from oxidative phosphorylation (223). Rats with induced hyperthyroidism had an increased responsiveness to warfarin, but the authors cautioned that the effect may not have been at the cellular level (335). Dextrothyroxine was noted to prolong the prothrombin time in patients on Dicumarol and in patients on acenocoumarin (102, 281). Combined warfarin and dextrothyroxine therapy in 11 patients with hypercholesterolemia resulted in a greater hypoprothrombinemic effect than the administration of the anticoagulant alone, yet no alteration in the results of several liver function tests occurred (446). The correction of myxedema by liothyronine (L-triiodothyronine, Cytomel®) requires a reduction in the dose of anticoagulant drug because of the undue prolongation of the prothrombin time (634). However, when hypoprothrombinemia with bleeding occurs in hyperthyroid patients receiving propylthiouracil it is probably the result of a mix-up of Dicumarol tablets with the physically similar antithyroid tablets (75).

In 1964, the rates of decay of the vitamin K-dependent clotting factors were found to be dependent on the metabolic state of the patient (330). Studies of patients with hyperthyroidism or fever showed disappearance rates about 3 times faster than normal after a standard dose of coumarin anticoagulant (330). In 1967, D- and L-thyroxine administered to mice were said to inhibit the metabolism of Dicumarol, but the animals were killed 1 hr after anticoagulant administration and the drug concentrations measured were too low to be reliable determinations (542). In 8 normal persons D-thyroxine increased the hypoprothrombinemic response to Dicumarol but the plasma level of Dicumarol at 36 hr was the same as control values (542). It was claimed from further studies with warfarin in only one subject that the mechanism of potentiation is an augmentation of the anticoagulant affinity for its receptor site by the thyroxine preparation (576). While it was shown that thyroxine administered alone did not alter the level of the prothrombin complex, measured by the thrombotest, no studies were performed on the disappearance rates of the vitamin K-dependent clotting factors, either individually or collectively, during the simultaneous administration of thyroxine and anticoagulants (542). The reviewers conclude that the increased responsiveness to oral anticoagulant drugs in hypermetabolic states is probably the result of increased catabolism of the vitamin K-dependent clotting factors (327).

4. Psychologic factors. The inter-relationship between blood coagulation and psychologic states and stress has been observed for years, most notably at the beginning of this century with Rasputin's success, reputedly through hypnosis, with the hemophilic son of the Russian Czar (346). Since then many clinical observations of hemophilic patients have revealed the effects of emotion on the general bleeding tendency (10, 88) as well as that occurring after surgery and dental procedures (337). Experimentally, stress has been found to affect bleeding from capillaries (303) and large blood vessels (273). In animals on anticoagulant drugs it has been repeatedly demonstrated that while many kinds of stress,

including that produced by LSD (lysergic acid diethylamide) (339), resulted in marked hemorrhagic phenomena and death, no augmentation of the hypoprothrombinemic state occurred (338). The administration of adrenocorticotropin (corticotropin injection, U.S.P.) or adrenocorticosteroid to animals, either with or without anticoagulant drugs, resulted in a variety of hemorrhagic diatheses (611). However, no studies have conclusively shown adrenal mediation of the bleeding manifestations of stress in man.

The psychologic implications of anticoagulant therapy for both the patient and the physician have been well appreciated (62, 185). Candidates for long-term therapy must have sufficient reliability, intelligence, and emotional stability (546) since anticoagulant treatment has specific characteristics which can cause anxiety (157). Patients who have suffered a life-threatening illness (usually myocardial infarction) and then are placed on a potentially hazardous form of therapy (anticoagulants) are prone to develop emotional problems (305). In one anticoagulant clinic, various patients perceived the therapy as impairing a vital function (hemostasis) or as having magical properties ("a new heart"), responded with anxiety to any increase in anticoagulant dosage, were reminded every day of their illness by the therapy, suffered a psychologic displacement by a shift of focus from their illness to the drug, were forced to endure the necessary strictness and rigidity of the therapy, and required on cessation of therapy the reassurance they could live without the medication (305). In the same study the physician's anxiety stemmed from the ever-present danger of hemorrhage, the questionable value of the therapy, the lack of any immediate benefit of this prophylactic therapy, and the complexities of managing the pharmacodynamics of an inhibitor of blood coagulation (305). Other workers disagreed and were impressed by the relative lack of emotional problems and anxiety-producing tendencies of the treatment, found it often necessary to induce fear and anxiety to motivate their patients, and felt that the reported emotional reactions were artifacts of excessive discussion of anticoagulant therapy with a psychiatrist (99, 602).

While the oral anticoagulants are commonly employed to prevent thromboembolic disorders, occasionally they are used to produce factitious disease (589), to commit suicide (254), or to accomplish murder (267, 411). Cases reported as acquired idiopathic hypoprothrombinemia may well have been due to surreptitious ingestion of an oral anticoagulant drug (137a). On rare occasions these drugs are dispensed in error by a pharmacist (293), or are confused with other medications (75). In addition patients with a false resistance to oral anticoagulants due to a surreptitious noningestion of the drug have been observed (423); the diagnosis was confirmed by finding a low or absent plasma level of the anticoagulant drug followed by appropriate discussion with the patient. Although seldom reported, surreptitious ingestion of oral anticoagulants must be more common than is generally recognized. Up to 1962, less than a dozen cases had been reported (433). In 1965, 10 cases were reported from 2 anticoagulant centers for a 15-yr period (72), and in 1966 12 cases over a 5-yr period were reported by another group who since have found 8 additional cases (429). The great majority of the patients were connected with the medical profession, usually as nurses, but

at least 7 of the patients had previous anticoagulant therapy (72, 429). The most frequent findings were cutaneous bleeding, hematuria, and a markedly prolonged prothrombin time.

The psychiatric aspects of surreptitious ingestion of anticoagulant drugs have not been well studied (153), but most of the patients are intelligent and conscientious (429). In contrast to malingerers and hysterics, their disability was not directed toward material gain. It has been suggested that these patients, unlike hysterics, are capable only of limited psychologic repression and dissociation, and when the threshold of mental conflict is exceeded they are driven to a consciously determined symptomatic solution, whether or not the original motivating situation is consciously appreciated (234).

B. Drugs alleged to increase the response

1. Salicylates. These analgesics reportedly increase the responsiveness to oral anticoagulant drugs (368, 547, 552). Hemorrhage from mucous membranes has long been observed as a toxic effect of salicylates (60, 321). In 1941, the chemical similarity of salicylate and Dicumarol and the discovery that salicylic acid was the primary degradation product of bishydroxycoumarin suggested that the anticoagulant might derive its effectiveness *in vivo* by conversion to salicylic acid (318, 547). In 1943, it was shown that salicylates in large amounts produced hypoprothrombinemia in rats on a low vitamin K diet when measured by a 1:8 plasma dilution of the one-stage prothrombin test (321, 325). This finding was confirmed in man (377, 556) and rabbit (274b), even when the diet was not deficient in vitamin K. Only slight prolongation of the undiluted prothrombin time was observed in patients receiving 1.3 to 5.3 g or more daily of acetylsalicylic acid (501). By 1949, monographs on anticoagulant therapy cautioned clinicians in the use of salicylates in patients on Dicumarol although no studies of the combination had apparently ever been performed in man (358, 557).

In 1954, 5 therapeutically anticoagulated patients given 5.0 g of acetylsalicylic acid daily for 10 days showed little or no effect in the P and P modification of the one-stage prothrombin test (275). In 1961, 17 therapeutically anticoagulated patients given 2.4 g of acetylsalicylic acid daily showed a detectable prolongation of a 1:8 plasma dilution of the one-stage prothrombin test, necessitating a reduction of the anticoagulant dosage (642). In 1968, administration of 1.95 g of acetylsalicylic acid daily for 7 to 10 days in 15 experiments involving 8 normal anticoagulated subjects did not prolong the undiluted one-stage prothrombin time except in 1 subject and could not be reproduced on repeating the experiment (427). In a second study 3.90 g of acetylsalicylic acid was administered daily to 5 of the same subjects; marked prolongation of the prothrombin time and signs of salicylism occurred in 2 subjects within 3 days (427). Another study showed no augmentation of the undiluted one-stage prothrombin time in 10 patients on long-term anticoagulant therapy who were given 3.0 g of acetylsalicylic acid daily for 10 days (607).

Hypoprothrombinemia may occur after massive salicylate ingestion but rarely causes bleeding unless it accentuates a hemorrhagic diathesis induced by

it simultaneously or initiated by an independent means (570). The additional diathesis may be increased capillary fragility (189), thrombocytopenia (509), decreased aggregation of platelets (174), decreased adhesiveness of platelets (48), liver disease (43), or oral anticoagulant therapy (499). Vitamin K can correct the hypoprothrombinemia induced by salicylates in experimental animals (325) and man (553), but if reduction of the prothrombin complex activity is not the main cause of hemorrhage, vitamin K therapy may be ineffective unless the other effects of salicylates on hemostasis are also antagonized by the vitamin (570). We conclude that the danger of moderate aspirin therapy, up to 3 g a day, during long-term anticoagulant therapy arises not from an augmentation of the hypoprothrombinemia but from its local action on gastric mucosa and its systemic effects on hemostasis (160).

2. Phenylbutazone. The pyrazole derivative phenylbutazone, N.F., B.P. (Butazolidin®), which does not alter blood coagulation when given alone, markedly potentiates the hypoprothrombinemic effect of the oral anticoagulant drugs. The first case was reported in 1956 (562); since then many cases of serious hemorrhagic complications have been reported for the combination (162, 188, 295). The most frequent serious complication is massive gastrointestinal hemorrhage associated with peptic ulceration (230, 369). The mechanism for this ulcer diathesis is unclear as phenylbutazone does not stimulate acid secretion by the stomach experimentally (614). Furthermore, the effect is not simply the result of direct erosion, as gastric changes also occur experimentally with parenteral administration of the drug (308). In one study phenylbutazone was said to impair the secretion of mucus by the canine gastric antrum, but it was not shown whether this finding explains the gastric mucosal injury by the drug (371). Phenylbutazone can also augment bleeding by its direct effect on primary hemostasis: it diminishes the collagen-induced release of platelet constituents (397).

The mechanism whereby pyrazolone derivatives potentiate the hypoprothrombinemic effect of the oral anticoagulants is not clear. It is not impaired liver function or altered vitamin K metabolism (86, 236). One group reported that phenylbutazone decreased the plasma half-life of Tromexan in one patient by delaying renal excretion of the anticoagulant (562), although Tromexan is not normally excreted unchanged in the urine and its metabolites have no anticoagulant activity (90). In 1965, another derivative, oxyphenbutazone (Tandearil®), was reported to retard the disappearance of Dicumarol from plasma (652). From these results (562, 652) it was suggested that enhancement of the anticoagulant effect might result from pyrazolone inhibition of the hepatic enzyme activity that metabolizes the coumarin drugs (122, 647).

Conversely, in 1964, it was hypothesized that phenylbutazone might accelerate the metabolism of the coumarin drug by displacing it from plasma proteins, thereby making more free anticoagulant available to its site of biologic action in the liver (82, 84). In 1967, it was shown that when the spectrophotometric measurement of the anticoagulant level in plasma was corrected for the optical contamination of phenylbutazone present, the plasma concentration and biologic half-life of warfarin were markedly less when the subjects were additionally given

400 to 500 mg of phenylbutazone than when they were given warfarin alone (7). In both the Dicumarol-oxyphenbutazone study (652) and the Tromexan-phenylbutazone study (562) the spectrophotometric measurement of the anticoagulant may not have been corrected for the optical contamination by the pyrazolone compound (7). Phenylbutazone markedly displaced warfarin from plasma albumin *in vitro* (7), a finding confirmed by others (577). In 1968, these experiments were repeated and the previous findings were confirmed in 6 normal subjects (431) by means of a fluorometric assay for warfarin (114) that is not influenced by the presence of phenylbutazone (431). These findings have been confirmed with phenprocoumon, although the specificity of the fluorometric assay of the anticoagulant was not studied (550). To account for the lowered plasma levels of warfarin in the presence of a marked increase of hypoprothrombinemia, it was suggested that phenylbutazone displaces warfarin from its binding sites on plasma albumin and makes more free anticoagulant available to the drug-metabolizing enzymes and to its sites of biologic action in the liver (7, 431). Conversely, in the dog phenylbutazone, a stimulator of hepatic microsomal activity, lessens the hypoprothrombinemic response to oral anticoagulants; the species difference was said to result from a reduced affinity of canine plasma albumin for the anticoagulant (360a). This hypothesis was confirmed in experiments with equilibrium dialysis by finding a 5-fold lesser association constant for the binding of warfarin to canine than to human albumin (426a). Apparently, the phenylbutazone-induced stimulation of warfarin metabolism is more important in the dog, while the greater binding with human albumin indicates that the phenylbutazone effect on warfarin transport is dominant in man (360a, 426a). The reviewers find at least 3 mechanisms for the hemorrhagic complications of phenylbutazone therapy superimposed on an oral anticoagulant regimen: an induction of peptic ulceration, an inhibition of primary hemostasis, and an augmentation of the hypoprothrombinemia.

3. Heparin has a marked effect on the one-stage prothrombin test. This naturally occurring mucopolysaccharide compound owes its anticoagulant activity to a strong electronegative charge that on interaction with clotting factor proteins, particularly thrombin, inactivates them reversibly (183, 272, 460). The anticoagulant of the leech, hirudin, also has an antithrombin mechanism of action (142, 192, 385). The clinical use of heparin in thromboembolic disease was received with initial enthusiasm (117, 283) but it is currently viewed with reservation both for arterial (111) and for venous disease (145). The difference, based on the results obtained, is reflected in the mode of use of heparin; its first use was prophylactic, to prevent thromboembolic disease (118), whereas its more recent use has been therapeutic, to treat existing thromboembolic or vascular disease (2).

The problem with heparin administration during oral anticoagulant therapy originates from their combined effect on the one-stage prothrombin test (150, 255, 310, 331). When the total coagulation effect is not appreciated by the clinician on stopping the heparin but continuing the dosage of oral drug, the prothrombin time shortens toward normal values because the dosage of the oral

anticoagulant by itself is not sufficient (388). One purveyor of heparin claimed the prothrombin time was affected only when the whole blood clotting time was over 40 min and alleged the problem could be avoided by determining the prothrombin time just before the next heparin dose (367). More recent data contradicted this assertion: any prolongation of the whole blood clotting time by heparin may affect the prothrombin time, even in the absence of prior hypoprothrombinemia and particularly in patients with recent myocardial infarction (2, 149, 388). However, heparin has little or no effect on the P and P test, because the plasma is diluted 10-fold, and in one modification heparin is routinely added to the test system to control glass activation (636).

If the clinician waits for the biologic effect of heparin to wear off to ensure accurate measurement of the prothrombin time, the patient will not be "anticoagulated" at all for some time. Tissue adsorption of heparin and its latent effect on blood clotting from intramuscular or subcutaneous routes are less predictable and often cumulative, a circumstance that vitiates the accuracy of a prothrombin test (657). As the end point of most coagulation tests is the observation of a solid fibrin clot resulting from the uninhibited action of thrombin on fibrinogen, the blood specimens for these tests should be drawn when the heparin has disappeared completely from the patient's plasma (657). The addition of just 0.2 unit of heparin per ml of normal human plasma *in vitro* markedly prolongs the partial thromboplastin time and significantly prolongs the one-stage prothrombin time. At a heparin concentration of 1 unit/ml, the prothrombin time is markedly prolonged (657). A 10,000-unit dose of heparin administered intravenously to a 70-kg adult with a 3,000-ml plasma volume will result theoretically in an initial plasma heparin concentration of 3 units/ml which will disappear from the plasma with a half-life of about 1½ hr (657). Thus, there is considerable documentation of a significant effect of heparin on the prothrombin time, which can be minimized during combined anticoagulant therapy only by giving the heparin intravenously and by drawing the blood for the prothrombin test just before the next heparin dose. A definitive study in man on the coagulation effect of the superimposed heparin therapy during either acute or chronic hypoprothrombinemia of oral anticoagulant therapy has not been reported.

4. Sulfonamides and antibiotics. The administration of sulfonamide and antibiotic drugs to patients on oral anticoagulants may potentiate the hypoprothrombinemia. In 1938, the synthesis of vitamin K by the intestinal bacteria of chickens was demonstrated (19), and in 1942, the sulfonamide drug sulfaguanidine, given orally, was shown to reduce the growth rate and prolong the one-stage prothrombin time (12.5% plasma) in young rats (63). Para-aminobenzoic acid counteracted both effects but vitamin K counteracted only the hypoprothrombinemic effect of sulfaguanidine. Rats and dogs given a single massive dose of sulfaquinoxaline (sulfabenzpyrazine), 0.4 g/kg body weight, showed marked prolongation of the prothrombin time 24 hr after administration and a moderate prolongation with a reduced dose, 0.2 g/kg body weight (392, 549). In both studies vitamin K could either prevent or reverse this action. In 1956, it was shown that 0.06% sulfaquinoxaline fed to chicks for 7 days prolonged the

clotting time and produced hemorrhagic lesions; vitamin K reduced the clotting time but did not prevent the hemorrhagic effect (287). Thus, sulfonamides in massive doses cause a rapid hypoprothrombinemic effect, simulating the action of an oral anticoagulant. In moderate doses a slower hypoprothrombinemic effect allegedly results from reduction of vitamin K-producing bacteria in the intestine, although the reviewers were unable to find any reports of direct bacteriologic verification of this latter point.

By 1954, treatment with antibiotics was said to cause a marked increase in sensitivity of response to oral anticoagulants (448, 647). It was reported that patients "highly resistant" to oral anticoagulants could be rendered sensitive to this therapy by simultaneous administration of antibiotics (448). In 1962, the administration of several antibiotics in therapeutic doses to patients on long-term anticoagulant therapy significantly reduced the percent of activity of the P and P$_1$ test in 11 of 28 patients (352). In rabbits the administration of massive doses of neomycin sulfate potentiated the Dicumarol-induced hypoprothrombinemia and the administration of vitamin K negated the antibiotic effect within 24 hr (363). Studies of chicks fed oxytetracycline (Terramycin®) showed that the antibiotic reduced intestinal bacteria (23). In 1965, administration of therapeutic doses of paromomycin (Humatin®), a "bowel-sterilizing" antibiotic, to 6 normal human subjects reduced intestinal flora but did not alter the whole or dilute (8-fold) one-stage prothrombin test (373). In another study, 10 patients on long-term anticoagulant therapy were given 4.0 g neomycin sulfate daily for 21 days, about twice the dose recommended for infectious diarrhea; no significant prolongation of the prothrombin time occurred (603). Thus, most well controlled experiments studied by the reviewers indicate that sulfonamides and antibiotics have little effect on the prothrombin time of patients on long-term anticoagulant therapy, unless (section II A 1) both dietary and intestinal sources of vitamin K are eliminated simultaneously (190, 226).

5. Clofibrate and anabolic steroids. Clofibrate (ethyl chlorophenoxyisobutyrate) potentiates the hypoprothrombinemic effect of oral anticoagulants. In 1963, the hypolipemic agent Atromid®, a combination of clofibrate and the steroid hormone androsterone, was found to augment the hypoprothrombinemic effect of warfarin and phenindione (419). The investigators suggested as the mechanism of action displacement of the anticoagulant from its binding site on plasma protein, thereby increasing its concentration in the liver (600). In the same year several hemorrhagic episodes resulting from the combination of clofibrate and anticoagulant were reported (528). It was soon found that both the antilipemic effect and the anticoagulant augmentation could be obtained with a preparation containing only clofibrate (Atromid-S®) (239). It was suggested that the augmentation of the anticoagulant effect might be related to the hypolipemic effect of clofibrate, particularly on reduction of the plasma and hepatic levels of the lipid-soluble vitamin K (409). The same investigators stated that patients with hypercholesterolemia require 2 to 4 times the usual anticoagulant dose to maintain a therapeutic effect, a circumstance that suggested to them hypervitaminemia K. Administration of high fat diets to animals resulted in a "hyper-

coagulable state," measured by the one-stage (671) and two-stage prothrombin tests (667), and in a 10-fold increase in the warfarin dose required to develop hypoprothrombinemia (307). Since similar augmentation of anticoagulant therapy also occurred with other antilipemic substances, such as D-thyroxine (195) (section II A 3) and C-17-alkylated steroids (194), the mechanism was considered a general hemostatic phenomenon associated with any antilipemic agent (195). This hypothesis suggested that the rate of synthesis of the prothrombin complex in patients on oral anticoagulants is limited by the availability of vitamin K, which becomes less when plasma lipids are reduced (195, 409).

Some aspects of these various theories have been tested. While clofibrate was shown to displace warfarin from human plasma albumin *in vitro* (577), no alteration in the blood level of anticoagulant drug could be detected *in vivo* after a single dose of Dicumarol (542) or a single or repeated doses (21 days) of warfarin (427). Patients given clofibrate were just as sensitive to oral anticoagulants whether the level of serum lipids fell or not (419). Clofibrate administered without concomitant anticoagulant therapy had no effect on the activity of the plasma clotting factors, measured by the thrombotest (542). While studies have shown that the augmentation of the hypoprothrombinemic effect of oral anticoagulants in patients with thyrotoxicosis results from an increased turnover of the vitamin K-dependent clotting factors (330), no studies have been reported on comparative turnover rates during anticoagulant therapy in the presence and absence of D-thyroxine or clofibrate. When the data become available, the theory that these drugs cause an increased affinity of the anticoagulant receptor site for the coumarin drugs (see section IV A) may become tenable (542). The reviewers find no satisfactory explanation, that has been experimentally verified, for the augmentation of oral anticoagulant effects by clofibrate or any other hypolipemic agent.

Anabolic steroids, like the C-17-alkylated derivatives of testosterone, increased the hypoprothrombinemic effect in patients on long-term anticoagulant therapy (194, 391a, 615). Previous observations showed that these anabolic compounds produced abnormalities in some liver function tests, particularly increased sulfobromophthalein retention and elevated serum transaminase levels (359, 676). In 1963, significant augmentation of the hypoprothrombinemic response to a single dose of warfarin was observed after administration of the anabolic steroid methandrostenolone (methandienone, B.P., Dianabol®) to 8 normal subjects for 14 days (486). As the plasma elimination rate of warfarin remained unaltered in these experiments, the investigators suggested that the augmented response results from an increased turnover rate of the coumarin-sensitive clotting factors (488). It is interesting that a nonalkylated anabolic steroid, quinbolone [17 β-(1-cyclopenten-1-yloxy)androsta-1,4-dien-3-one], did not affect hepatic function or the response to oral anticoagulants (487).

6. Miscellaneous drugs. Alcohol, U.S.P. (ethyl alcohol), allegedly augments the hypoprothrombinemic effect of oral anticoagulant drugs. The most common cause of bleeding in anticoagulated patients may be chronic alcoholism (354). The contraindication of this therapy in alcoholic patients is not based on pharma-

cologic considerations but upon the sporadic unreliability of these patients (186, 622). Two case reports claimed that alcoholic beverages decreased the responsiveness to Dicumarol necessitating an increase in the anticoagulant dosage, but the dosage was not monitored by assays of drug in blood (422). Interestingly, an increased rate of clearance of warfarin from the circulation of alcoholic patients has been reported (292a). A large single dose of alcohol infused into the stomach of rats had no effect on blood coagulation measured by the thrombotest (638). Twenty patients on long-term anticoagulant therapy were given a large dose of alcohol or an alcoholic beverage over a 1-hr period; the one-stage prothrombin time was unaltered (637). In 1966, 10 patients on long-term therapy received very large single doses of alcoholic beverages (521); little change in the prothrombin time or in the specific prothrombin activity (factor II) occurred, but the activity of factors VII and X fell during the subsequent 24 hr. In 1 alcoholic patient the anticoagulant effect of warfarin was enhanced by *disulfiram* (Antabuse®) (530). Thus, the reveiwers deem that the occasional use of alcoholic beverages in moderation by patients on long-term anticoagulant therapy bears little risk.

Phenyramidol (Analexin®), a muscle relaxant, was found in 1965 to markedly potentiate the oral anticoagulants. Potentiation was first detected in 2 patients, 1 of whom had a generalized hemorrhagic diathesis (101). A subsequent study of 10 patients on long-term anticoagulant therapy verified this effect; therapeutic doses of phenyramidol augmented the one-stage prothrombin time in all 10 within 3 to 7 days (101). Furthermore, the drug had no effect on the prothrombin time of 10 subjects not receiving anticoagulants. In 4 normal subjects phenyramidol increased the blood levels and the half-life of Dicumarol after a single dose of anticoagulant, but it was not determined whether or not the Dicumarol assay was free of interference by phenyramidol (574). From these data as well as the impact of phenyramidol on the metabolism of other drugs, phenyramidol was said to inhibit the metabolism of oral anticoagulants by hepatic microsomal enzymes (575).

Cinchophen is a well known hepatotoxin that has been replaced in therapeutics by safer cinchona derivatives (165). In 1954, cinchophen dramatically intensified the hypoprothrombinemia in 4 patients on long-term anticoagulant therapy, 1 of whom died of hemorrhage (275). However, it was concluded that the augmentation was not a direct hepatotoxic effect because the delayed onset of the cinchophen potentiation resembled that of the oral anticoagulants, the potentiation disappeared soon after discontinuance of cinchophen, and there were no clinical findings of impaired liver function (275).

Benziodarone (Amplivix®), an antianginal drug, caused bleeding complications among patients on oral anticoagulants in 1963 (485). Potentiation seemed to occur with only certain oral anticoagulants, but individual patient responsiveness as the basis for the variation was not assessed. In 1969, benziodarone was administered to 29 patients on long-term therapy; 9 had prolongation of the prothrombin time that required a reduction in anticoagulant dosage (619). In

5 of the 9 patients ecchymoses and marked weight gain occurred during administration of benziodarone. Five normal subjects were given a large single dose of Tromexan before and 6 days after administration of benziodarone; all exhibited a highly significant retardation of the anticoagulant disappearance rate from plasma, although the specificity of the Tromexan assay in these experiments was not determined (619). Eleven patients on long-term anticoagulant therapy were given amiodarone (Cordarone®), a new drug belonging to the same benzofuran group as benziodarone, daily for about 10 weeks; no effect on the prothrombin time occurred (619).

Monoamine oxidase (MAO) inhibitors allegedly potentiate the effect of oral anticoagulants in man (622). The original MAO inhibitor, iproniazid, was withdrawn from use because of its hepatotoxicity and adverse effect on liver function tests (120). In 1962, several MAO inhibitors administered to rabbits were found to prevent the usual shortenings of the one-stage prothrombin time induced by injection of epinephrine or ingestion of cholesterol (560). Monoamine oxidase inhibitors interfere with platelet adhesiveness *in vitro* (271). Co-administration of warfarin and an MAO inhibitor to 34 rabbits resulted in considerable augmentation of hypoprothrombinemia (139), but administration of the MAO inhibitor to rabbits already anticoagulated did not cause significant potentiation. The hypoprothrombinemic effect of Tromexan in rats was augmented by iproniazid and abolished by reserpine (260). In 1965, a study of several combinations of of oral anticoagulants and MAO inhibitors in rats showed variable potentiation of the hypoprothrombinemic effect with some of the combinations (514). However, the reviewers were unable to find any studies or even case reports in man on the potentiation of oral anticoagulation by any MAO inhibitor.

Quinidine sulfate, U.S.P., has been said to act synergistically with oral anticoagulant drugs in an occasional patient (300, 573). In 1 case of alleged quinidine-induced hemorrhage, in which no pharmacodynamic studies were performed, the bleeding could have resulted from marked responsiveness to the anticoagulant because of severe hepatic congestion in the patient (203). The administration of 1.6 g quinidine/day to 10 patients on long-term anticoagulant therapy resulted in no changes at all in the prothrombin times (605).

In rats, *6-mercaptopurine* (Purinethol®) significantly augmented the hypoprothrombinemic response to oral anticoagulant drugs (97); no studies of man have been reported. *Acetaminophen*, N.F. (paracetamol, B.P., Tylenol®), which probably has no effect (27, 606) in patients on oral anticoagulants, significantly prolonged the prothrombin times of patients on long-term warfarin therapy (28). The reported inhibition of Tromexan metabolism in man by the antidepressant drug *methylphenidate*, N.F. (Ritalin®) has yet to be confirmed by demonstrating the specificity of the Tromexan assay used and the enhancement of its anticoagulant action (202). The simultaneous administration of *morphine sulfate*, U.S.P., or *meperidine hydrochloride*, N.F., pethidine, B.P. (Demerol®) with large single doses of oral anticoagulants in rats and rabbits significantly increased the hypoprothrombinemic effect (259a).

III. DECREASED RESPONSIVENESS: NONHEREDITARY FACTORS

A. Pregnancy and the newborn state

The impact of oral anticoagulant therapy on the gravid state is complex. One of the physiologic consequences of pregnancy is the development of a "hypercoagulable" state (459). The changes observed in the coagulation parameters include increased activity of plasma clotting factors (292), increased platelet adhesiveness (237), increased levels of plasma phospholipids (531), increased plasminogen levels (412, 678), decreased levels of fibrinolysin (207, 412), and decreased urinary excretion of urokinase (678). The high incidence of thromboembolic complications in pregnancy may reflect the presence in pregnancy of the classic factors of Virchow's triad: the venous stasis secondary to the enlarging gravid uterus, the hypercoagulable state, or the development of a vascular disease like thrombophlebitis (13, 626).

In the last century, the circulating level of fibrinogen was known to be elevated during pregnancy (144, 469). In 1939, prothrombin was said to be elevated because of a shortened one-stage prothrombin time (599), but the rise determined by the two-stage assay was less pronounced (277). This discrepancy between the one-stage and two-stage methods for the elevation of "prothrombin" during pregnancy was resolved in 1952 by specific factor assays which showed an elevation of factor VII but not of factor II activity (329). Factor V was found to be unaffected during pregnancy (13), while factors IX (513), X (459), and VIII (292) rose significantly to about twice normal activity.

In the 1920's pregnant cows with little evidence of sweet clover disease often had offspring that died from hemorrhage either *in utero* or in the neonatal period (526, 541). In 1942, pregnant rats were found resistant to the hypoprothrombinemic effects of a standard dose of Dicumarol (181). The newborn pups of bitches fed Dicumarol just before parturition had a one-stage prothrombin activity strikingly lower than that of the mother (494). Similar results were found in newborn rabbits (304). Although expectant mothers have been safely treated with Dicumarol (175, 356, 673), 2 cases of fetal anomaly (293a) and many cases of fetal or neonatal death with multiple hemorrhage have occurred with oral anticoagulant therapy (170, 215, 353, 457, 469a, 490, 515, 533, 601, 628). While the latter reports suggested that Dicumarol might cross the human placental barrier, this phenomenon was not demonstrated until 1965, when nearly equal concentrations of the drug, administered before delivery, were found in mother and child immediately post partum (534). On rare occasions oral anticoagulants have been used as an abortifacient, the tablet form by paramedical personnel (119), and an extract of a coumarin-containing plant (*Ferula communis*) by women in rural areas (407).

It was recognized long ago that newborn calves and newborn pups of rats and dogs were much more susceptible to Dicumarol than mature animals (318, 494, 541). Numerous studies have shown that newborn infants with bleeding disorders have a very low level of prothrombin complex activity (hemorrhagic disease of the newborn) (81). While the response to minute doses of vitamin K_1 is

often dramatic, the use of vitamin K_3 can result in kernicterus (1, 631). Despite the high incidence of maternal thromboembolic disorders in the immediate postpartum period, there was a hesitancy to use anticoagulants because of the possible migration of the drug across the blood-breast barrier in a susceptible nursing infant (74). The administration of massive doses of Dicumarol (177) or warfarin (66) to rats induced hypoprothrombinemia presumably caused by mammary transfer of the anticoagulant to the suckling rats. In a series of 125 lactating mothers given anticoagulants prophylactically, the one-stage prothrombin times of all the nursing infants were unaffected even when the mothers showed definite resistance and required higher doses of Dicumarol than normal subjects (74). Direct testing of maternal milk for warfarin in 2 patients on a therapeutic anticoagulant regimen showed no unchanged drug (427). Previous reports on the excretion of coumarin drugs in maternal milk may have represented the detection of biologically inactive drug metabolites (176, 217). Finally, in 4,000 mothers given oral anticoagulants prophylactically, all of the breast-fed infants remained asymptomatic throughout the period of therapy (191).

Oral anticoagulants should be used cautiously during pregnancy because of their ability to pass the placental barrier. However, this contraindication does not extend to heparin. In studies of 4 pregnant guinea pigs and 7 pregnant women given heparin intravenously, no anticoagulant effect was detected in the neonatal blood immediately post partum when the maternal whole blood clotting time was significantly prolonged (184). The factors that might retard the rate of placental transfer of heparin are its large molecular size (16,000), its high degree of ionization (pKa = 1.8), and its marked aqueous solubility (623). For required treatment with anticoagulants during pregnancy, heparin is the drug of choice (622).

B. Diuresis and uremia

Diuretic drugs decrease the responsiveness to oral anticoagulant drugs in man. In 1954, the diuretic mersalyl (Salyrgan®) was found to lessen the hypoprothrombinemia of Dicumarol in dogs (178). In 1963, the administration of chlorthalidone (Hygroton®) to patients on long-term anticoagulant therapy was found to increase factor VII activity toward normal levels in most patients and prothrombin complex activity in some patients, but factor X activity remained unchanged (624). After administration of mersalyl sodium (Mercurgan®) and hydrochlorothiazide, U.S.P. (Esidrix®) a marked general increase in the activity of the intrinsic clotting system was observed during the diuretic phase of a grossly edematous patient in congestive heart failure (161). In rats, the administration of hydrochlorothiazide alone raised the activity of the one-stage prothrombin test above 100%, yet when it was given simultaneously with oral anticoagulants it augmented the hypoprothrombinemic effect (98). In 1968, administration of chlorthalidone to 7 normal subjects decreased the responsiveness, determined by measurement of the one-stage prothrombin time and the activities of clotting factors II, VII, IX, and X, to single and repeated doses of warfarin (8). When the lesser fall in clotting factor activity was corrected for the

loss of plasma volume during the diuretic phase, no significant difference was seen between the control and the chlorthalidone experiments (441). In these experiments no changes occurred in the plasma level of warfarin and essentially no unchanged warfarin was found in the urine during chlorthalidone treatment (8). There are no experimental or clinical data to support the statement that diuretic agents prevent the accumulation of anticoagulant drug in the liver by causing more rapid elimination of the drug in the urine (622, 624). The reviewers conclude that the lessened response to oral anticoagulants after treatment with diuretic drugs probably results from the concentration of the clotting factors in the blood or from the reduction of congestion in the liver with consequent increase in synthesis of vitamin K-dependent clotting factors.

Uremia and chronic renal disease without complication usually do not increase the responsiveness to oral anticoagulants, despite statements to the contrary (14, 145, 464). The contraindication to this therapy in patients with impaired renal function had its inception in the early experimental work. In 1942, a marked increase in responsiveness to Dicumarol was produced in dogs by injection of uranium acetate and by bilateral ureteral ligation (68). Bilateral nephrectomy produced similar results in rats (520). In 2 patients with anuria the prothrombin time was prolonged but became normal on return of renal function (532). Determination of the absence of unchanged Dicumarol in the urine of animals (444) and man (651) suggested renal metabolism of the anticoagulant to some investigators (68, 532). In 1952, 9 patients with chronic renal disease showed no altered responsiveness to Dicumarol, had no episodes of bleeding, and required an average anticoagulant dose for long-term treatment (532). These same investigators (532) also criticized the relevance of the previous work with impaired renal function because all renal function was eliminated in the animals (68, 520) and anuric patients and because a compound (uranium acetate) toxic to both kidney and liver was used (68).

In 1966, patients with chronic renal disease had an average response to a large single dose of warfarin, even when the prothrombin complex activity was reduced before administration of the anticoagulant (5). The significantly increased volume of distribution for warfarin that was found in the uremic patient may be one explanation for the relative lack of response. Thus, we caution the use of oral anticoagulants in patients with impaired renal function not because of any increase in responsiveness to oral anticoagulants but because of the bleeding diathesis of uremia itself (105) and its superimposition on the hypoprothrombinemic effect of coumarin drugs (164).

C. Drugs alleged to decrease the response

1. Hypnotics and sedatives. Many hypnotic drugs decrease the hypoprothrombinemic response to oral anticoagulant drugs in man and animal (154). In 1942, chlorobutanol, U.S.P. (Chloretone®) was noted to antagonize the hypoprothrombinemic effect of Dicumarol in rats (46). A similar antagonism was first observed in man in 1955 when several barbiturate compounds were found to decrease the hypoprothrombinemic effects of Tromexan (32). Similar findings

were reported for glutethimide, N.F. (Doriden®) (113, 224). In 1960, phenobarbital, U.S.P. (Luminal®) was found to increase the activity of hepatic enzymes that were involved in the metabolism of drugs (110). The antagonism by barbiturates of the hypoprothrombinemic effect of oral anticoagulants was correlated with lower plasma levels of the coumarin drugs (136). However, no antagonism and no change in drug levels occurred when the anticoagulant was given intravenously (136). The microsomal fraction of liver homogenates from immature rats treated with large doses of phenobarbital showed a several-fold increase in the amount of Dicumarol metabolized *in vitro* (122). The pretreatment of normal dogs with glutethimide, barbiturates, or meprobamate, N.F. (Equanil®, Miltown®) resulted in decreased blood levels of warfarin, but no coagulation studies were performed (262). A lesser hypoprothrombinemic response to oral anticoagulants associated with decreased plasma coumarin levels has also occurred with chloral hydrate, U.S.P. (Noctec®, Somnos®), in man (123, 613), and perhaps with ethchlorvynol, N.F. (Placidyl®) (279), but not chlordiazepoxide, N.F. (Librium®) (362, 613), diazepam (Valium®) (362), or haloperidol (Haldol®) (416).

In 1969, a detailed study showed that 3 days of pretreatment with a hypnotic dose of heptabarbital (Medomin®) in 10 normal human subjects caused a highly significant lessening of the hypoprothrombinemic effect of Dicumarol, both with oral and intravenous administration of the anticoagulant (6). The results with the oral form of Dicumarol were more marked, and 41% of the anticoagulant dose was recovered as unchanged drug in the stool compared with 17% when heptabarbital was not given. This suggested an interference with Dicumarol absorption as another factor in the interaction of anticoagulant and hypnotic drugs (6). A significant lessening of the hypoprothrombinemic effect was also found with warfarin given orally (524) and intravenously to 9 normal human subjects pretreated for 3 days with heptabarbital (432). The biologic half-life of warfarin in plasma was much shorter after heptabarbital (113), whereas its apparent volume of distribution remained unchanged (432). However, oral administration of 1 or 2 doses of barbiturates did not affect the hypoprothrombinemic response to oral anticoagulants in 27 patients (535).

The initial explanations for the occurrence of the barbital antagonism with only the oral route of administration of anticoagulant were a difference in metabolic pathways for oral *versus* intravenous coumarin drug (136), an enhancement of anticoagulant metabolism by hepatic portal filtration with the oral route of administration (645), and a hindrance to the metabolic disposition of the anticoagulant by its nearly complete protein binding in plasma (216). However, the more recent experiments with intravenous administration of coumarin drugs showed a definite reduction by barbital pretreatment of both the hypoprothrombinemic effect and the plasma levels of anticoagulant (6, 432, 613). Studies of rats pretreated with phenobarbital correlated the increased excretion of nonmetabolized drugs with the enhanced bile flow (231, 296). Griseofulvin, U.S.P. (Fulvicin®, Grifulvin®, Grisactin®) given orally antagonized the hypoprothrombinemic effect of warfarin orally in 3 out of 4 patients (125); increased recovery of unchanged griseofulvin in the stool after barbital pretreat-

ment has been observed with the oral administration of both drugs (522). There are several reported ways in which one drug interferes with the absorption of another drug: direct chemical combination (cholestyramine resin or kaolin compounds) (198), alteration of the mucosal barrier of the intestine (colchicine) (643), or alteration of intestinal transit time (riboflavin) (314).

Although hypnotic drugs reduce the responsiveness to oral anticoagulants, if the prothrombin time of the patient and anticoagulant dose are regulated accordingly and then the hypnotic drug is stopped, the prothrombin time will lengthen significantly and bleeding may ensue (123, 347, 518). Rats treated with oral anticoagulants suffered from spontaneous and often fatal hemorrhages when additionally subjected to barbiturates or chlordiazepoxide (339a). The interaction of hypnotic and anticoagulant drugs endures as a challenging frontier for the investigator.

2. Adrenocorticosteroids and miscellaneous drugs. Beginning in 1950, an increased incidence of thromboembolic complications was reported in patients receiving adrenocorticotropin (ACTH) or adrenocorticosteroids that was associated with some evidence of "hypercoagulability" of the blood (115, 116, 163). Detailed coagulation studies confirmed this suggestion of a "hypercoagulable state" in patients with Cushing's syndrome (pathologic hypersecretion of adrenocorticosteroids) and in patients given large daily doses of prednisone, U.S.P. (288, 454). In 24 patients on long-term Dicumarol therapy, the administration of prednisone significantly shortened the silicone whole blood clotting time (370). It is said that patients on adrenocorticosteroids require a larger dose of oral anticoagulant drug to achieve therapeutic hypoprothrombinemia (104), but detailed studies are not available.

Other drugs may decrease the responsiveness to oral anticoagulants. *Aminopyrine* decreases the response in guinea pigs (650). *Cholestyramine* (Cuemid®, Questran®) interferes with the absorption of warfarin in man (198). *Estrogens* and *oral contraceptives* may increase the required oral dose of anticoagulant (543), perhaps because of a "hypercoagulable state" (413, 679) like that reported for pregnant women (459) and gravid rats (483); *males* were reported to require a larger dose of oral anticoagulant than the nongravid woman but in this report the doses were not corrected for body weight or body surface area (372). The one-stage prothrombin response to oral Dicumarol in rabbits was decreased by oral (179) but not intravenous (493) *methylxanthines* (547). *Multivitamin preparations* containing vitamin K were said to reduce the responsiveness to oral anticoagulants (165), but none of the 168 multivitamin preparations listed in the 1968 *Physician's Desk Reference* (466) contained any vitamin K! In the absence of cholestatic hypersensitivity to the drug, *phenothiazine tranquilizers* did not alter the clinical responsiveness to oral anticoagulants (259). Studies in guinea pigs with *reserpine*, U.S.P. and *chlorpromazine hydrochloride*, U.S.P., showed an increased responsiveness to a standard dose of acenocoumarin, whereas the antidepressant *desipramine* hydrochloride (Norpramin®) had no influence on the hypoprothrombinemic effect (648). *Antihistamines* reportedly decrease the response to oral anticoagulants (165), but the reviewers could not document this assertion.

IV. ALTERED RESPONSIVENESS: HEREDITARY FACTORS

A. Increased responsiveness

There are no published data on any heritable condition associated with an increased hypoprothrombinemic response to oral anticoagulant drugs. Theoretically, this response could result from genetic conditions that might cause an increased concentration of anticoagulant drug or a decreased concentration of vitamin K in the whole patient or at the drug receptor site, or from a decreased activity of the vitamin K-dependent clotting factors. One might predict the mechanisms to be a decreased metabolism of the anticoagulant drug; a decreased body store of vitamin K because of its decreased production or absorption or increased metabolism; a decreased production or increased metabolism of the vitamin K-dependent clotting factors; or a receptor site with increased affinity for the anticoagulant drug or decreased affinity for vitamin K, or both.

B. Decreased responsiveness

1. Increased rate of elimination of the anticoagulant. The role of genetic factors in the disposition of oral anticoagulants was first observed in certain rabbits that showed considerable variation in their responsiveness to Dicumarol (100, 571). Further study of the rabbit suggested that the resistance to Dicumarol might be inherited as a recessive mendelian character (444), but the genetic data were later considered inadequate and never published (318). In 1964, a study of 700 rabbits demonstrated that the sensitive and resistant responses to Dicumarol represented distinct populations within the normal distribution (379). Resistant rabbits given Dicumarol orally (440) and intravenously (274a) were found to have far less drug in their plasma than responsive rabbits because of faster biotransformation of the drug.

In man, marked variation was recognized in the response to and physiologic disposition of Dicumarol (651), Tromexan (87), phenindione (544), and warfarin (436). In 1964, the role of genetic factors for the metabolism of Dicumarol in man was suggested by the finding of a positive sib-sib correlation for the drug half-life in plasma (389). In 1968, genetic control of the disposition of Dicumarol in man was established by finding very similar plasma half-lives for the anticoagulant in identical twins but very different half-lives in fraternal twins (620). Female rats have higher levels in plasma of the coumarin-sensitive clotting factors, and after administration of a large single dose of warfarin they return more quickly to normal levels even though these rats metabolize the anticoagulant more slowly and their median lethal dose for warfarin is one-third that of males (484). Genetic control of the disposition of warfarin in rats was demonstrated by selectively inbreeding 2 lines of animals from a random-bred colony of Sprague-Dawley rats in which the response of factor VII to the anticoagulant was used for selection (489). One line, which was characterized by a rapid metabolism of warfarin (5 hr), showed little hypoprothrombinemic response, while the other line, characterized by a slow metabolism (30 hr), showed a marked response.

Acquired resistance to oral anticoagulant drugs has been described, albeit

without documentation, in patients whose resistance was overcome by administration of an oral antibiotic to alter the intestinal flora (448), by switching to another oral anticoagulant (580), or by parenteral administration of the drug (579, 581). In 1964, a patient with the nephrotic syndrome required 40 mg of warfarin a day orally or intravenously, about 6 times the average daily dose, to achieve therapeutic hypoprothrombinemia (316). Severe hypoalbuminemia was also present and the rate of warfarin clearance from plasma (6.5 hr) was 7 times faster than the rate in normal subjects, even though no unchanged warfarin was found in the urine. In 1968, a similar resistance was found in another patient with the nephrotic syndrome, although detailed pharmacodynamic studies could not be carried out (507). Possibly, the rapid half-life of the drug and the relative lack of biologic effect are related to the lack of serum albumin in these patients. Thus, resistance to oral anticoagulants on the basis of rapid drug metabolism has resulted from selection of the extreme of a normal distribution (rabbits), from selective inbreeding (rats), and from disease (man).

The wide variations of response to drugs in man are attributable to the inheritance of multiple genetic factors that control their metabolism and biologic effect (389). This difference of responsiveness usually gives rise to a unimodal frequency distribution (309). However, when the response can be segregated into clearly distinct groups (bimodality), a single gene effect should be suspected and appropriate family studies should be carried out (172, 290).

2. Changes in sensitivity of the receptor. Hereditary resistance to the oral anticoagulant drugs has been discovered in man and rat. In 1960, resistance to the rodenticidal effect of warfarin was described in wild rats (*Rattus norvegicus*) trapped in western Scotland (73). Studies of these rats in the laboratory by forced ingestion of the warfarin in food verified the tolerance (127). Additional locations of resistant rats were found in Denmark (341) and Wales (147). In 1964, the first human kindred with a genetically determined resistance to oral anticoagulants was described (435). The propositus required 145 mg of warfarin/day, or 50 standard deviations above the average daily dose, to achieve a therapeutic effect. The metabolism of the oral anticoagulants in the 3 generations of the family was entirely normal; other than the marked resistance to oral anticoagulants only an increased responsiveness to the antidotal action of vitamin K was found (428). In 1966, a genetic basis consistent with a single autosomal gene controlling the dominant character was established for the warfarin resistance in the rats from Scotland (173). The resistant mutants in Denmark were less viable because when the selective pressure imposed by oral anticoagulants was removed, the proportion of resistant rats decreased markedly in 4 years (342). In 1968, the genetic factor for the anticoagulant resistance in rats from Wales (220, 478) was successfully bred into laboratory strains of rats through 6 generations of backcrossing. The resistant rats of the sixth generation were shown to have blood and hepatic levels of anticoagulant similar to those of normal Sprague-Dawley rats after a large single dose of warfarin (440, 478). Homozygous resistant rats, in the absence of any administered warfarin, had a marked increase in vitamin K requirement (249). But the metabolism of radio-

active vitamin K and radioactive warfarin in these rats disclosed no significant differences from normal rats (37, 597).

In 1969, the second reported kindred of hereditary resistance to oral anticoagulant drugs in man was described (426). The daily dose of warfarin for the propositus was 90 mg, 30 standard deviations above the average. The detailed genetic study showed normal drug levels in the blood and marked resistance to the hypoprothrombinemic effect of a large single dose of warfarin in 18 of 41 family members, which duplicated the findings of the first kindred. In addition, male-to-male transmission of the resistance was demonstrated in 4 sons from 2 fathers (427); this rules out location of the gene on the X chromosome. The data for the 2 kindred, 24 resistant out of 49 members, are consistent with the dominant expression of a single autosomal gene (426).

The mechanism for pharmacogenetic phenomena can be divided into 2 broad categories. One is a genetic polymorphism of drug metabolism, as occurs with succinylcholine chloride, U.S.P., and isoniazid, U.S.P. (172, 290). The other category is a genetic polymorphism for drug response, as occurs with primaquin phosphate, U.S.P., and the oral anticoagulants. In the heritable resistance to warfarin for both man and rat the metabolism of the anticoagulant drug and vitamin K-dependent clotting factors were normal (440). The results in man and rat were consistent with a mutation of the receptor site that had an altered affinity for the oral anticoagulants or for vitamin K (220, 248, 428, 435, 440). The propositi of both human kindreds and the resistant rats were studied by a vitamin K competition technique while chronically hypoprothrombinemic; all were found to be extremely responsive to very small amounts of exogenous vitamin K (426, 428). The same strain of resistant rats was also studied by a vitamin K repletion technique, and the heterozygous resistant rats were found to have a slightly greater vitamin K requirement than normal rats while the sickly homozygous resistant rats had a markedly greater vitamin K requirement (248). From the vitamin K-warfarin competition experiments in resistant man, an increased affinity of vitamin K for the receptor site was proposed (440), whereas in the vitamin K repletion experiments in the resistant rats, a decreased affinity of vitamin K was suggested (249). However, all the data for man and rat signify that the basic mechanism for resistance is a genetic mutation of the vitamin K-warfarin receptor site that is transmitted as a single gene controlling the dominant character. The genetic mutation in the heterozygous state appears to have no deleterious effect on the persons or rats affected. What effect resistance to the action of the coumarin anticoagulant drugs may have on survival in man is unknown. The favorable effects on survival in resistant wild rats, however, is potentially dangerous, as the genetic trait appears to be monofactorial and fully dominant in heterozygous rodents and apparently does not hinder the reproductive capacity of the affected animals. Therefore, the biochemical mechanism for this extraordinary resistance forms an important area for further pharmacogenetic research in man and rat. Finally, it is intriguing to speculate that the study of these genetic variants may clarify the normal mechanism of action of oral anticoagulant drugs (159a).

V. UNALTERED RESPONSIVENESS: OTHER FACTORS

In this review we have considered primarily the determinants that clearly alter the response to the oral anticoagulant drugs. Factors with little documented effect on the response that have not been discussed include achlorhydria (311), climatic conditions (384), diabetes mellitus (361), digitalis, U.S.P. (547), nicotinic acid (niacin, N.F.) (25), irradiation (565, 621), tolbutamide, U.S.P. (103, 480), vitamin C (ascorbic acid, U.S.P.) (46) except in scorbutic guinea pigs (137, 593), indomethacin (Indocin®) (390, 665), chloroquin phosphate, U.S.P. (238), malignancy (213), edema (361), polycythemia, epinephrine, U.S.P., sitosterols (Cytellin®) (25), cyclamate (253a), acetylcholine, atropine sulfate, U.S.P., smoking, sleep, and hyperventilation (362).

VI. SUMMARY

The *general determinants* of the response to oral anticoagulant drugs are critically reviewed, and the specific physiologic, pathologic, and pharmacologic factors that increase and decrease the responsiveness to these agents are examined with needful scrupulosity. Because the experimental data in laboratory animals supporting the clinical application of anticoagulant drugs are controversial, their employment in patients is essentially empirical and based on clinical trials. The basic premise of oral anticoagulant therapy is that interference with hemostasis reduces morbidity and mortality from thromboembolic disorders. The latest experimental research indicates that blood coagulation involves the occurrence of both enzymatic and stoichiometric reactions in the conversion of circulating precursors to activated clotting factors and in the formation of complexes composed of one clotting factor acting as a prosthetic group for another, respectively. Thrombogenesis and coagulation are similar processes in that thrombus formation is a hemostatic event that occurs intravascularly. In the development of a thrombus the blood platelet is now known to occupy the quintessential position. Since the platelet plug forms the bulk of an arterial thrombus, the best therapeutic strategy should be antithrombotic agents that interfere with the adherence of platelets to vessel walls and to each other. Since the blood clot forms the bulk of a venous thrombus and a pulmonary embolus, the best therapeutic strategy should be anticoagulant drugs that interfere with the coagulation of blood. In practice, oral anticoagulants have little effect in arterial thrombotic disease, in contrast to their significant therapeutic effect in venous thrombotic disease and in emboli from mural thrombi of the heart.

The mechanism of action of oral anticoagulants proceeds from their competitive effect with vitamin K activity at a ribosomal level or at a subsequent step in which the conversion of peptide precursors to the vitamin K-dependent clotting factors is promoted by the vitamin and retarded by the anticoagulant. The pharmacodynamics in man of sodium warfarin, the most prescribed oral anticoagulant drug in the United States, include rapid gastrointestinal absorption and slow plasma elimination, a biologic effect lasting for days, a significant correlation between the plasma drug levels and the degree and duration of

hypoprothrombinemia, a high degree of binding to plasma albumin, an apparent volume of distribution the size of the albumin space, and a lack of urinary excretion of the unchanged drug. Hydroxylation is the major pathway of warfarin and Tromexan metabolism in man and rat. Thermodynamic analysis of the warfarin-albumin binding process studied by equilibrium dialysis and by direct calorimetry shows an exothermic reaction with negative free energy, which suggests hydrogen bonding and hydrophobic bonding in the interaction. The lesser albumin binding, the absent anticoagulant effect, and the urinary excretion of the hydroxylated metabolites suggest that the addition by metabolism of a polar hydroxyl group onto the coumarin nucleus reduces its hydrophobic bonding to plasma albumin and hepatic receptor sites. The speed of onset of the "antithrombotic effect" of oral anticoagulants, the therapeutic reduction of factors II, IX, and X, is the same whether therapy is initiated with or without a loading dose of the drug. Although many modifications of the one-stage prothrombin test have been proposed, therapy is best controlled by the original method.

Many nonhereditary factors may cause *increased responsiveness* to oral anticoagulant drugs. A deficiency of one of the sources of vitamin K, from a lack of either dietary ingestion or intestinal synthesis, increases responsiveness, and a deficiency of both sources causes hypoprothrombinemia. The potentiation of the anticoagulant effect in patients with liver disease is not altered by administration of vitamin K. The increased responsiveness in patients with hypermetabolic states such as fever and hyperthyroidism probably results from increased catabolism of the vitamin K-dependent clotting factors. Many kinds of stress in animals, with or without concomitant anticoagulant therapy, result in hemorrhage. Anticoagulant drugs have been used surreptitiously to produce factitious disease, suicide, and even murder. Surreptitious noningestion of anticoagulants can be falsely interpreted as resistance to anticoagulants. The potential danger of moderate aspirin therapy, up to 3 g a day, during long-term therapy with anticoagulants results not from augmentation of the hypoprothrombinemia but from the local action on gastric mucosa and the systemic effect on hemostasis. Hemorrhagic complications of phenylbutazone therapy superimposed on an oral anticoagulant regimen are caused by induction of peptic ulceration, inhibition of hemostasis by platelet aggregation, and augmentation of the hypoprothrombinemia. Heparin increases the responsiveness to oral anticoagulants; this interaction can be only minimized by giving heparin intravenously and by drawing the blood for the prothrombin test just before the next heparin dose. Most well controlled studies indicate that sulfonamides and antibiotics have little effect on the prothrombin time of patients on long-term therapy with anticoagulants unless both dietary and intestinal sources of vitamin K are eliminated simultaneously. Compounds that augment the response to but not the plasma levels of oral anticoagulants do so by an obvious alteration of hepatic function (alkylated anabolic steroids), by a subtle alteration of hepatic function detectable only by a decreased rate of synthesis of the vitamin K-dependent clotting factors (perhaps clofibrate), or by a reduction of

lipid-soluble substances that may include vitamin K (several antilipemic agents). As ethyl alcohol seldom augments the hypoprothrombinemic effect of long-term anticoagulant therapy, the occasional use by patients of alcoholic beverages in moderation bears little risk.

The *decreased responsiveness* to oral anticoagulants in pregnant women results from increased activity of several clotting factors. Oral anticoagulants should be used cautiously during pregnancy because of their ability to cross the placental barrier, but they may be used liberally post partum, if indicated, as there is little evidence to indicate mammary transfer of the drug to the nursing infant. Barbiturates lessen the hypoprothrombinemic response through reduction of coumarin blood levels by enhancing metabolism (all oral forms) as well as by decreasing absorption of the anticoagulant (Dicumarol). The decreased response to oral anticoagulants after treatment with diuretic drugs can result from a concentration of the clotting factors or from a reduction of congestion of the liver, both as a result of the diuresis achieved. Uremia and uncomplicated renal disease usually do not increase the responsiveness to anticoagulants.

Hereditary factors can alter the responsiveness to oral anticoagulant drugs. However, there are no published data on any heritable condition associated with an increased hypoprothrombinemic response to oral anticoagulant drugs. Two kinds of resistance to oral anticoagulants have been described. Resistance because of rapid metabolism of the drug occurs in normal rabbits from selection of the distribution extreme of anticoagulant metabolism, in rats from selective inbreeding, and in man from disease. In rats and in two human kindred resistance in the presence of normal drug metabolism has been described on the basis of a genetic mutation of the vitamin K-anticoagulant receptor site that is transmitted as a single autosomal gene controlling the dominant character of the resistance. What effect this resistance may have on survival is unknown. The lack of therapeutic action of these drugs may be a disadvantage to man, but relative resistance to compounds of this type, perhaps occasionally encountered in his environment, would be advantageous. The study of these genetic variants could elucidate the normal mechanism of action of oral anticoagulant drugs.

VII. CONCLUSION

Members of the medical profession may behold oral anticoagulants either as valuable or as valueless therapy (205). Though resistive to both extremes, we commend the study of these drugs to all students of pharmacology and to all practitioners of therapeutics. These agents can serve as a model system of pharmacologic action because of the ease of quantifying the anticoagulant effect and the drug itself in man. Perhaps the oral anticoagulant drugs have become a paragon among pharmaceuticals for probing the mechanisms of pharmacologic problems that beset our patients.

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