A Guide to Anticoagulant Therapy

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This article* has been prepared to provide guiding principles and practical recommendations for the proper use of anticoagulant drugs. No consideration has been given to the indications for therapy or to the merits of the various agents in the prophylaxis or treatment of specific diseases. Also, fibrinolytic agents alone, or in conjunction with anticoagulant therapy have not been included because sufficient clinical experience has not yet been accumulated to permit recommendations concerning their use. This article, therefore, has been designed to assist the physician who has already decided to invoke treatment.

Initial Screening

It is assumed that a complete history, physical examination, and certain minimal laboratory studies will be performed on any patient for whom anticoagulant therapy is considered. Since hemorrhage is the greatest hazard even in well-controlled therapy, a careful search for actual or potential causes of bleeding must precede the administration of these drugs.

The hemostatic mechanism constitutes one of the lifesaving homeostatic functions. If it fails, one incurs the risk of serious disability or death from hemorrhage. Not only should one know whether a patient is actively bleeding at the time he is seen, but also whether the patient has ever had excessive bleeding whenever he has been hurt, cut, or subjected to other trauma. A history of repeated or episodic bleeding is crucial in alerting the physician to the possibility that his patient is a bleeder. Several specific questions are helpful in this regard: Are there bleeders in the family? Has the patient had frequent nosebleeds? Do his gums bleed on brushing the teeth? Has the patient experienced unusual hemorrhage following dental extraction? Is there easy bruising manifest by ecchymoses without apparent injury? Is there excessive menstrual flow, or has there been excessive hemorrhage after childbirth? Are there bleeding hemorrhoids, or other sites from which the patient has bled from time to time? Does bleeding stop promptly after cuts and scratches? Is there a history of severe hemorrhage after surgical procedures, such as tonsillectomy? A "no" to all these questions readily excludes hemorrhagic disorders in the vast preponderance of individuals.

In addition to the recognition of a bleeding diathesis, a good history can suggest dietary defects leading to hemorrhage, such as lack of vitamin C, or evidence of prior overt bleeding such as from peptic ulceration, esophageal varices, colitis, polyps, or past ocular or intracranial hemorrhage. The history may also reveal significant information concerning hypertensive, hepatic, and renal disease, each of which may be associated with hemorrhage, as well as the likelihood of major surgery in the immediate future. Finally, careful questioning will yield information concerning

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Table 1

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Other names</th>
<th>Clotting phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>Third, fourth</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
<td>Second</td>
</tr>
<tr>
<td>III</td>
<td>Thromboplastin</td>
<td>Second</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium</td>
<td>First, second, † third</td>
</tr>
<tr>
<td>V</td>
<td>Ac-globulin, labile factor, proaccelerin, accelerator factor, plasma prothrombin converting factor</td>
<td>First, second</td>
</tr>
<tr>
<td>VII</td>
<td>Proconvertin → convertin, stable factor, serum prothrombin conversion accelerator (SPCA), prothrombinogen, autoprothrombin I, † prothrombokinase</td>
<td>Second</td>
</tr>
<tr>
<td>VIII</td>
<td>Antihemophilic factor (AHF), Antihemophilic globulin (AHG), Hemophilic factor A, platelet cofactor I, thromboplastinogen, thromboctolysin</td>
<td>First</td>
</tr>
<tr>
<td>IX</td>
<td>Plasma thromboplastin component (PTC), Christmas factor, hemophilic factor B, autoprothrombin II</td>
<td>First</td>
</tr>
<tr>
<td>X</td>
<td>Stuart factor, Stuart Prower factor</td>
<td>First, second</td>
</tr>
<tr>
<td>Profibrinolysin</td>
<td>Plasminogen</td>
<td>Fourth</td>
</tr>
<tr>
<td>Fibrinolysin</td>
<td>Plasmin</td>
<td>Fourth</td>
</tr>
<tr>
<td>Hageman factor</td>
<td>HF</td>
<td>First</td>
</tr>
<tr>
<td>Plasma thromboplastin</td>
<td>PTA</td>
<td>First</td>
</tr>
<tr>
<td>antecedent</td>
<td>Hemophilic factor C</td>
<td>First</td>
</tr>
</tbody>
</table>

* Nomenclature of clotting factors, designated by Roman numerals, is in accordance with recommendations of the International Committee on Nomenclature of Blood Clotting Factors.

chronic medication, such as steroids, that may predispose to hemorrhage.

On physical examination acute massive bleeding may be recognized by the signs of shock or by the local painful accumulation of fluid in a joint, muscle, or retroperitoneal areas, often with associated fever. Pallor, ecchymoses, adenopathy, or hepatosplenomegaly may suggest a disorder possibly associated with hemostatic defects. If the blood pressure cuff is allowed to remain inflated half way between systolic and diastolic pressure for 5 minutes, abnormal fragility of the capillaries (Rumpel-Leede test) may be revealed.

Minimal laboratory procedures should include a hemoglobin determination, a blood smear to establish the presence of an adequate number of platelets, a urinalysis, and a stool examination for gross and occult blood.

This initial screening is simple and requires little additional time. The recognition of hemorrhage or a tendency to bleed, however, does not constitute a blanket contraindication to anticoagulant therapy. Clinical judgment is required at all times to balance the anticipated hazards of hemorrhage against the threat of thromboembolic disease.

**Hemostatic Mechanism**

An understanding of the coagulation sequence is necessary to the proper use of anticoagulant drugs. The most recent schema is divided into four phases (tables 1 and 2). The intravascular fluidity of blood is believed to be dependent upon a delicately balanced state in which procoagulant forces are counteracted by anticoagulant forces. Under certain circumstances, this equilibrium may be disturbed, resulting either in overt clinical bleeding, on the one hand, or excessive thrombus formation, on the other.

Hemostasis depends, however, not only on
the fibrin clotting system and on the quantitative and qualitative aspects of platelet function, but also on the integrity of the vascular tree, especially in the microcirculation. While blood clotting factors affected by anticoagulant agents are fundamental in hemo-

stasis, equally important, and too often disregarded, are the nonequilibrium aspects of the hemostatic mechanism, both in the screening of patients and as a cause of hemorrhagic complications attending therapy. In some instances, malfunction of mechanisms other than coagulation, e.g., vascular, may explain hemorrhagic phenomena occasionally encountered, even when clotting factors have been maintained at so-called "therapeutic levels." The physician should be particularly alert to this possibility in those disorders known to be associated with hemorrhage on a vascular basis, namely, hypertension, diabetes, nutritional inadequacy, vasculitis, congenital malformations, infection, allergic and anaphylactic disorders, and polycythemia. Finally, certain occupations predisposing to trauma may present special hazards in individuals receiving anticoagulant therapy.

Anticoagulant Agents

The two most widely used agents are hepa-

rin ("direct" anticoagulant) and the couma-

rin derivatives and related compounds ("indirect" anticoagulants). Their use requires comprehension of their physiologic effects and of the numerous variables influencing their action, as well as familiarity with the guides to administration, contraindica-

tions, and appropriate antidotes. The drug response for a given patient may vary even from day to day, as a consequence of numerous physiologic factors as well as pathologic processes. Accordingly, treatment must be individualized.

Heparin

Heparin exists in the various tissues of the body, particularly the liver and lung, and most likely in the mast-cell granules. Following its discovery in 1916 by McLean and Howard, many properties of this naturally occurring sulfated mucopolysaccharide have been elucidated, and its general clinical usefulness has been thoroughly investigated since it was first employed as an anticoagulant by Murray and by Crafoord. The effectiveness of synthetic congeners (heparinoids) has been explored, but it is generally accepted that their toxic side-reactions make them undesirable except in rare instances where the natural heparins cannot be used.

Action

The anticoagulant action of heparin, attributed to its highly negative charge, depends upon its inhibition of certain interactions involved in thromboplastin elaboration, in thrombin formation, and in thrombin disposition (table 2). The latter effect occurs either by enhancement of the thrombin inhibitory action of the natural plasma antithrombin, or by another as yet obscure thrombin inhibitory mechanism. In appropriate doses, heparin also prevents platelet aggregation and, in addition, is said to potentiate the fibrinolytic system.

Other biologic effects of heparin include its lipemia-clearing action, its enhancement of vascular permeability, its blockade of the local and generalized Shwartzman and Arthus phenomena, its inhibition of trypsin and hyaluronidase, its inactivation of serotonin and certain snake venoms, and its increase in the L-\(^{131}\)triodothyronine uptake of red blood cells.

Even in large doses heparin has no effect on blood pressure (except in rare instances), peripheral or coronary circulation, respiration, body temperature, renal and hepatic function, blood chemistry, or red and white blood cells.

Absorption, Fate, and Administration

Within 15 minutes after the intravenous injection of heparin, 30 per cent is found in the liver, where it is inactivated by heparinase. Within 30 minutes, 2 per cent, and within 24 hours, 40 per cent, appears in the urine—largely as a breakdown product, "uroheparin." Excretion occurs via both glomeruli and tubules, and the amount thus eliminated is substantially reduced by renal
injury. The importance of both liver and kidney function in the disposal of heparin warrants caution in its use when disease of these organs is present. Heparin, in contrast to coumarin drugs, does not pass the placental barrier, and does not appear in milk.

One milligram of the crystalline standard heparin-sodium salt is equivalent to 100 U.S.P. units or 130 international units. The specific activity of highly purified material from different species varies widely, depending on the molecular chain length.
ANTICOAGULANT THERAPY

Administered in the form of a soluble salt, heparin is best given intravenously, preferably intermittently, but also by continuous infusion. The subcutaneous and intramuscular routes have also been used. By mouth, sublingually, or applied dermally the agent has little, if any, effect.

The anticoagulant action is proportional to the dose, varies from patient to patient, and becomes evident within minutes following intravenous administration. The over-all result is retarded coagulation manifested by the elevated clotting time of freshly shed blood. This is the cardinal laboratory guide to dosage. The bleeding time, which reflects more the response of the microvascular tree to trauma, is unaffected.

The anticoagulant effect of heparin is short lived; for example, 50 mg. may prolong the clotting time for 2 to 4 hours following intravenous administration. Peak prolongation occurs within minutes after injection, after which the clotting time gradually returns to normal. Coagulation is less retarded when heparin is given by intramuscular or subcutaneous routes, and the duration of the effect, although more prolonged, is not infrequently erratic. This prolonged effect following intramuscular and subcutaneous administration is a disadvantage when one wishes to shift from heparin to a coumarin compound, because sustained elevated blood levels of heparin interfere with the prothrombin time determination, as well as with the reversal of its anticoagulant effect with protamine, should this be necessary.

Toxicity

Heparin is essentially nontoxic. Rarely, alopecia may occur. In certain individuals the drug may cause untoward reactions, which range from mild urticaria to sudden, severe hypotension, respiratory distress, and chest pain. Most rarely, transient thrombocytopenia has been observed shortly after its administration. Heparin does not interfere significantly with the extravascular deposition of fibrin, and hence does not retard the healing of surgical wounds.

Antidotes

The anticoagulant action can be promptly reversed, milligram for milligram, by an equivalent amount of protamine sulfate. This markedly basic protein has a strong affinity for heparin, thus combining with it to give a relatively insoluble product. Protamine is therefore extremely useful as an antidote. Protamine is available in 1 per cent solution in 5-ml. vials. It is slowly administered intravenously after dilution in physiologic saline, in an amount equivalent to the last dose of heparin but never in excess of 50 mg. Its antiheparin effect lasts about 2 hours. Some heparin activity may reappear, if the anticoagulant was administered in large doses shortly before it was deemed necessary to reverse its action. Blood or plasma transfusions, although of value in replacing blood lost from hemorrhage, are not specific antidotes against heparin, as they are against the coumarin drugs.

Coumarin Derivatives and Related Compounds

Since the discovery by Link and Campbell over 20 years ago of bishydroxycoumarin (Dicumarol) and its relation to hemorrhagic spoiled sweet clover disease of cattle, significant advances have been made in the basic and therapeutic aspects of this and related substances, termed "indirect anticoagulants." Following the first therapeutic use of bishydroxycoumarin by Meyer and Bingham, and Butt and Allen, more than 100 chemically related compounds have been studied, but only a small number are generally accepted as reasonably safe agents (table 3).

Action

There is considerable agreement that all these agents depress the identical specific plasma clotting constituents concerned with the formation of thrombin from prothrombin (table 2). In contrast to heparin, they have no direct action on coagulation in vitro. Generally referred to as "prothrombinopenic" drugs, they lead after a variable latent period to a reduction in plasma factors II (prothrombin), VII (proconvertin), IX (plasma thromboplastin component), and X (Stu-
art). By thus retarding and limiting the rate and amount of thrombin formation, clotting is slowed.

There is no universal agreement concerning the sequential order in which the specific factors become decreased. It is generally accepted, however, that factors VII and X decline before prothrombin. Observed variations in the onset of factor IX depression (frequently the last to be so affected) may be related to the use of different drugs, dosage schedule, and assay technics. Although the anticoagulant effect was initially attributed to diminution of plasma prothrombin per se, it now appears that depression of the other factors is at least equally important.

Coumarin-type compounds also decrease platelet adhesiveness, depress the activity of several platelet enzymes, and alter the fibrinolytic system. Other biologic actions include increased capillary permeability, increased coronary blood flow, increased red cell uptake of radioactive thyroxin, interference with oxidative phosphorylation, and increased urinary uric acid excretion.

Presumably all these agents act on the liver, where they are fixed, metabolized, and degraded at variable rates, followed by excretion through the renal and biliary tracts. Although the precise mechanism by which the "prothrombinopenic" effect is induced is obscure, it is likely that synthesis of the clotting factors is inhibited. This effect is in equilibrium with the patient's stores of vitamin K1, a nutrient obtained from intestinal bacterial synthesis as well as by ingestion of vitamin K1-containing foods such as mature grains, spinach, cauliflower, cabbage, and tomatoes. The coumarin drugs, resembling the vitamin in chemical structure, are thought to compete as an antimetabolite with the vitamin, for the apoenzyme functioning in the synthesis of the pertinent clotting factors.

Absorption, Fate, and Administration

Important in the use of these drugs is consideration of the various factors that influence the individual reaction to a given dose. For example, bishydroxycoumarin, the earliest agent used, and the one concerning which most knowledge has been accumulated, is

Table 3
Properties of Some Coumarin-Type Compounds

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Usual initial doses (mg.)</th>
<th>Usual maintenance doses (mg.)</th>
<th>Usual onset of peak activity (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumarin</td>
<td>Bishydroxycoumarin</td>
<td>Dicumarol</td>
<td>300-600</td>
<td>25-100</td>
<td>1.5-3</td>
</tr>
<tr>
<td></td>
<td>Ethyl biscoumacetate</td>
<td>Tromeran</td>
<td>1500-2400</td>
<td>600-900</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Cyclocumarol</td>
<td>Cumopyran</td>
<td>100-200</td>
<td>15-40</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Acenocoumarol</td>
<td>Sintrom</td>
<td>10-20</td>
<td>3-5</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Pheonprocoumon</td>
<td>Liquemar</td>
<td>20-40</td>
<td>3-5</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>Winterin</td>
<td>Mareoumar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Athrombin-K</td>
<td>40-60</td>
<td>5-10</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coumadin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pan Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indandione</td>
<td>Phenindione</td>
<td>Athrombin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Bindan</td>
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<td></td>
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<td>Danilone</td>
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<td></td>
<td></td>
<td>Dindevan</td>
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<td></td>
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<td>Dineval</td>
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<td></td>
<td></td>
<td>Indema</td>
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<td></td>
<td></td>
<td>Indon</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PID</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pindione</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diphenadione</td>
<td></td>
<td>Dipaxin</td>
<td>20-50</td>
<td>3-5</td>
<td>1-2</td>
</tr>
<tr>
<td>Anisindione</td>
<td></td>
<td>Miradon</td>
<td>500-700</td>
<td>50-150</td>
<td>1-2</td>
</tr>
</tbody>
</table>
ANTICOAGULANT THERAPY

relatively insoluble, is more slowly absorbed, is bound longer in the plasma, remains for more prolonged periods in the liver, and is degraded there more slowly than some of the other related compounds. Accordingly, its "prothrombinopenic" effect is slow in appearance, more retarded in reaching peak activity, more cumulative, and more slowly dissipated. At the other extreme is warfarin, which is very soluble, and indeed is the only agent that can be given intravenously, intramuscularly, and rectally, as well as by mouth. This may be particularly advantageous, for example, when for any reason oral intake is temporarily precluded during the course of therapy.

The solubility characteristics that affect absorption and transfer to the liver also bear on the question of whether a particular drug should be administered in single or multiple daily doses. Thus, it is believed by some that the more soluble agents such as ethyl biscoumacetate, warfarin, and indandione derivatives should be given in divided doses for optimal sustained effect.

The variables inherent in a given individual are to a great extent responsible for the difficulties in maintaining the prothrombic activity at the desired level during therapy. Their importance, however, cannot be overemphasized. These varying influences may be physiologic or may arise as a consequence of disease. Clearly the net effect of a given drug dose will depend somewhat on the initial stores of the pertinent clotting factors in both the circulation and extravascular depots and their rates of mobilization, as well as upon their rates of synthesis and turnover. The latter are measured in terms of hours in contrast to other plasma proteins, such as albumin with a half life of approximately 3 weeks. Accordingly, the momentary effect of an agent that only partially blocks synthesis of a factor that is being rapidly consumed, is subject to wide variations. On this basis alone fluctuation may be anticipated from day to day in a given individual.

Although the initial depressing effect of a single priming dose is fairly uniform for each compound, wide variations occur in the total duration of the effect among different individuals, and in a given subject from time to time. It should be noted that debilitated and cachectic individuals are very sensitive to these drugs. Variation in a given individual is also observed during the course of maintenance therapy. This has been attributed to fluctuations in gastrointestinal, hepatic, renal, and metabolic functions secondary to physiologic or pathologic disturbances. The physician should therefore be alert to possible changes in the state of these organs, particularly during long-term therapy. Other pathologic states also influence the reaction to these drugs; for example, individuals with fever or scurvy are said to manifest increased sensitivity to the coumarin-type agents.

Also, there is considerable experimental evidence indicating that the prothrombinopenic effects of the coumarin congeners, as measured by the prothrombin time and hemorrhagic tendency, are enhanced by stressful stimuli and adrenocortical hormones.

Mention has been made of the antagonistic relationship between vitamin K, and the "prothrombinopenic" drugs. The patient's nutritional state with regard to this fat-soluble vitamin will therefore influence considerably the degree of "prothrombinopenia" induced. Body stores of the vitamin, initial or periodically supplemented from intake, can influence the ebb and flow of the pertinent factors dependent on this nutrient for synthesis. Here again, the nature of the diet, hepatic function, gastrointestinal motility, and fat absorption as well as intestinal bacterial flora (which may be greatly influenced by antibiotics), will exert their effects.

Chemical methods for measuring many of the "prothrombinopenic" agents in the plasma are available. This may be valuable in those instances where obscure hypoprothrombinemia and bleeding are suspected to be a result of self-induced medication. Also useful in this regard is the fact that if a suspect chemical is administered to a test animal and
a hypoprothrombinemic state ensues, this constitutes strong evidence of the coumarin nature of the material, since few if any other agents give this biologic reaction.

Some properties of the many available coumarin-type anticoagulants are listed in Table 3. Measurement of the speed of the conversion of prothrombin to thrombin in a plasma sample is used as the guiding laboratory procedure for measuring their anticoagulant effect at any given time. Since it is not known which, if any, of the affected clotting components are paramount in the development of thrombosis, on the one hand, or of hemostatic failure during therapy, on the other, the practical laboratory tests most widely used are those that reflect the overall effects on clotting kinetics rather than a procedure that measures any single factor.

Although some anticoagulant effect of the "prothrombinopenic" agents is demonstrable within 24 hours after administration, peak activity may not be obtained until some time thereafter, depending upon the properties of the particular drug employed, the priming dose, and the metabolic processes described above.

Patients are occasionally encountered who are inexplicably resistant or sensitive to coumarin-type drugs. In addition, subjects have been observed who, after being steadily and satisfactorily maintained on a given drug for a long interval of time, will develop hemorrhagic phenomena coincident with a marked drop in prothrombic activity, especially during acute infections.

It may be summarily stated, especially in view of the many variables involved, that the physician must treat each patient on an individual basis. If he is not prepared to do this, he should not administer anticoagulants.

Toxicity

As with heparin, toxic reactions (aside from bleeding) to the coumarin-type drugs are rare. Nausea, vomiting, diarrhea, and leukopenia are sometimes observed. More serious, but nonetheless unusual, are hepatic and renal damage, fever, rash, jaundice, leuko-
weeks, should resumption of therapy be necessary. Although vitamin K₃ correction of drug-induced "prothrombinopenia" is fairly prompt, immediate reversal of the clotting defect can be attained by transfusion with blood, plasma, or plasma fractions* rich in the pertinent clotting factors. Because the involved factors are relatively stable, ordinary ACD banked blood, bank plasma, or lyophilized plasma are fully potent and will exert their effects almost immediately. Three units of blood or plasma should generally suffice, while the simultaneously administered vitamin K₃ will set in motion the regeneration of the respective clotting factors. In patients with limited cardiac reserve such volumes may be hazardous unless blood loss has been significant.

Contraindications to Anticoagulant Therapy

In general, anticoagulants should not be employed under the following circumstances: a hemorrhagic diathesis, severe hypertension, cerebrovascular hemorrhage, active ulceration or overt bleeding from the gastrointestinal, respiratory, genitourinary or pulmonary tracts, surgery of the central nervous system, inadequate laboratory facilities, and inadequate cooperation of the patient with the therapeutic regimen. In pregnancy the coumarin derivatives are generally contraindicated because of their ability to pass the placental barrier.

There are other contraindications that are somewhat less stringent. Here the urgency of therapy must be balanced against the risk of hemorrhage that is involved. These include moderate hypertension, diabetes, vasculitis, subacute bacterial endocarditis, renal and liver disease, surgery in general, but particularly of the biliary tract in the presence of hepatic failure, and surgery of the lung and prostate. Pericarditis complicating acute myocardial infarction deserves special consideration in view of the possibility of hemopericardium consequent to the use of the coumarin drugs. Extensive bleeding into the thyroid gland has also been observed in thyrotoxic patients who have received therapeutic while on anticoagulant therapy.

In addition there is a group of disorders in which adequate preparation before anticoagulants are given may reduce the hazards of therapy. These include: congestive heart failure, malnutrition, vitamin C and K deficiencies, ulcerative colitis, sprue, steatorrhea, and pancreatitis.

It is important to realize that this guide should not be taken too literally. The question as to whether in a given patient the need for anticoagulant therapy outweighs its hazards requires sound clinical judgment.

Questions and Answers

1. Question: Among Laboratory Tests* Currently Available, Which is the Most Satisfactory and Practical as a Guide to the Dosage of Coumarin-type Drugs?

Answer: Since the anticoagulant action of these agents is predicated upon their decreasing the concentration of factors II, VII, IX, and X (tables 1 and 2), the ideal test would be one that measures all of these activities in a simple, inexpensive procedure that is least susceptible to technical error. Until recently, the Quick whole-plasma prothrombin time, which measures all of these factors except IX, has been considered as best fitting these requirements, and most of our information regarding coumarin therapy has been obtained with this test. The "Thrombotest," recently devised by Owren, includes the measurement of factor IX, thus theoretically providing a more comprehensive assay of the pharmacologic effects of these drugs. It has the further advantage that it can be performed on capillary blood at the bed side. At present there is insufficient experience to state definitively whether the "thrombotest" is superior to the Quick prothrombin determination as a guide either to the antithrombotic action or the hemorrhagic complications of coumarin-type drugs.

2. Q. Why Are There So Many Different Techniques for Performing the Quick Prothrombin Time? What Method Is Considered Most Desirable?

*Details of the several tests referred to in this pamphlet are found in Coagulation of Blood. Methods of Study in the Bibliography.
A. Numerous variations are related to different thromboplastic extracts employed, technical differences in the actual mixing of reagents, the end point selected for a definitive result, and the interpretation of the observed clotting time in terms of the per cent prothrombin activity. For gauging the effect of the “prothrombinopenic” drugs, the determination on whole plasma by the original Quick procedure is generally considered best. One major point to be considered in the procedure is the potency of thromboplastic extract used. The material should give a prothrombin time on normal plasma of between 10 and 14 seconds. Less potent extracts are apt to give erratic results. The value on normal plasma in seconds should always be expressed side by side with that for the test plasma.

3. Q. Should the Results of the Prothrombin Determination Be Reported in Seconds, or Per Cent of Prothrombin Activity?

A. Either method is satisfactory. The advantage of reporting in seconds is that it provides an indication of the potency of the thromboplastin, and at the same time indicates whether the desired elevation in prothrombin time has been achieved. It should be elevated one and a half to two times the value of the control plasma. Another advantage in reporting the prothrombin values in seconds is that the results obtained in one laboratory can be compared with those obtained on the same patient in another laboratory, provided the control value of the other laboratory is known and the thromboplastin employed in the test is derived from the same species.

Reporting in per cent, on the other hand, permits a simple assessment of the day-to-day and week-to-week trend of the effect of the drug. For these reasons it is best to request both time and per cent values, even though this increases the amount of data to be recorded.

4. Q. What Are the Important Technical Factors in Obtaining and Processing Blood Samples for Prothrombin Time Determinations?

A. The observed prothrombin time in the Quick procedure reflects the concentrations of factors II, V, VII, X, as well as factor I (fibrinogen). Except for fibrinogen, all may be influenced by lapses in technic. If the vein is not entered directly in performing the venipuncture, if delay is encountered between drawing the blood into the syringe and thorough mixing with the anticoagulant, if tissue juice is drawn back even in minute amounts into the needle as a result of not entering the vein directly, or, if the needle slips out of the vein during blood withdrawal, factor VII may be activated, thus giving a falsely low (accelerated) prothrombin time. Conversely, prothrombin or factor V may be partly consumed as a result of such technical failure, giving a falsely elevated (retarded) prothrombin time. Under any of these circumstances, therefore, it is advisable to make a completely new attempt with another syringe and needle. A delay of more than 2 to 4 hours between the drawing of the blood and its analysis in the laboratory can result in a false determination on whole plasma because factor V is labile, especially at room temperature, and may deteriorate, thus yielding falsely elevated prothrombin times. This technical difficulty can be circumvented, however, by a modification of the Quick test in which ample amounts of factor V are added in the assay.

Q. How Often Should Prothrombin Times Be Performed?

A. This question has special significance with regard to “long-term” therapy. After the daily prothrombin determinations establish the individual dose requirements (usually in about a week), the tests can be spaced to every other day, subsequently to twice weekly and eventually once every 2 weeks. On “long-term” therapy, less frequent determinations are permissible but only after the physician has become sufficiently familiar with the patient’s needs, his stability, and after he is assured of the patient’s capacity and willingness to cooperate. If the results indicate stability, determinations can be safely performed every 2 weeks. There is some difference of opinion as to the advisability of longer intervals. Intervals longer than 3 weeks incur substantial risk of lack of adequate control. Determinations spaced at more than 4 weeks should be reserved for extremely few individuals under special circumstances.

For those patients contemplating an extended vacation, or whose occupation or other circumstances demand considerable travel, the doctor should refer the patient to a reliable physician elsewhere, or familiarize himself with laboratories in other cities where accurate determinations can be obtained for his patient.

6. Q. Why Do Prothrombin Times Fluctuate So Widely?

A. The many variables that influence the prothrombin time can be briefly listed as follows: the biochemical and physiologic properties of “prothrombinopenic” drugs, including their solubility, absorbability, transport and fixation in the liver; their speed of metabolism, degradation, and excretion; the nutrition of the patient with regard to vitamin K; the synthesis, original stores, and in vivo turnover rates of the various clotting factors affected; and pathologic processes in the recipient. Any of these may considerably and acutely vary in a given individual from time to time. Also to be considered are lapses in technic.

Circulation, Volume XXIV, July 1961
7. Q. What Is the Significance of the Term "Whole" as Contrasted with "Dilute" Prothrombin Time?

A. The term "whole" is applied to determination of the prothrombin time on whole plasma obtained from centrifuged oxalated or citrated blood. The observed value reflects the concentrations of factors I, V, II, VII, and X. Of these, the last three are influenced by the coumarin-type drugs. To eliminate test variations dependent on fibrinogen or factor V, several procedures have been devised in which these two factors are provided in optimal amounts to the test system by diluting the test plasma with adsorbed normal plasma (fig. 1). In this way a more reliable assay for the three coumarin-affected factors is provided. Moreover, such dilution permits more precise quantitation by setting the conditions of the test at a range where the prothrombin time can be more sharply correlated with the concentration of these clotting factors. The dilution of the test plasma with adsorbed normal plasma, rather than with physiologic saline, thus minimizes this possible error while providing a better endpoint.

8. Q. There Is Considerable Reference in the Literature to "One-Stage" and "Two-Stage" Methods of Measuring Prothrombin. What Does This Terminology Signify, and Has It Any Relevance to Anticoagulant Therapy?

A. The term "one-stage" refers to the commonly employed Quick procedure or modifications thereof, for measurement of prothrombic activity in one step: by the addition of thromboplastin and calcium to plasma, and measurement of the velocity of clotting (prothrombin time). The term "two-stage" applies to a procedure, originally devised by Seegers and colleagues, in which the prothrombin determination is made in two stages: in the first step, a suitably diluted sample of plasma is mixed with thromboplastin and calcium, which converts all the prothrombin to thrombin. In the second step, the amount of thrombin formed is then measured by its clotting of a standardized fibrinogen solution. This method, of great value in coagulation research, is specific for measuring prothrombin, but does not include the other factors influenced by the "prothrombinopenic" drugs. Since these other factors are thought to play an important role in anticoagulant action, the Quick one-stage procedure, by measuring more of the factors, is considered preferable as a practical guide to coumarin therapy.

9. Q. What Is the "P-P" Test of Owren? Is It Preferable to the Quick Test?

A. This is essentially a modification of the Quick one-stage procedure. Originally devised by Owren, it was intended to measure both prothrombin (factor II) and proconvertin (factor VII). We now know that it also includes factor X (Stuart). It is therefore as satisfactory as the Quick test for measuring these factors. The Quick procedure, however, gives additional information regarding factors I and V.

10. Q. What Is Meant by the Term "Therapeutic" Range of Prothrombin Activity?

A. Clinical experience indicates that an activity of 10 to 20 per cent of normal is compatible with normal hemostasis, assuming all other hemostatic functions to be normal: platelet count, vascular function, etc. To be reasonably certain that the activity does not fall below the lower level, in view of the normally experienced variations in activity (discussed in the text) the physician should strive
for an activity of 15 to 25 per cent of normal (approximately one and one-half to two times the control value in seconds). That this represents retarded coagulation is evident from the curve correlating prothrombic activity with the prothrombin time (fig. 1). At or below 20 per cent activity, the velocity of thrombin elaboration from prothrombin becomes progressively and rather sharply retarded. Although values below 10 per cent prothrombic activity give even slower speeds of clotting, such levels increase the risk of bleeding progressively as the prothrombin time rises. In reality the "therapeutic" range is defined in a negative sense; namely, the maximal reduction in prothrombic activity compatible with satisfactory hemostasis.

11. Q. What Is the Desired "Therapeutic" Level with Heparin?
A. Here again we are guided by experience. As with the coumarin drugs, the objective is maximal interference with coagulation with minimal risk of hemorrhage. When the clotting time is two times the normal value obtained in a given institution with its own particular technic and equipment, clotting is markedly retarded, yet there is no serious danger of bleeding. Temporary spikes above this level can also be tolerated without undue risk of hemorrhage. As with the prothrombin time, meticulous technic must be followed to avoid false clotting times: glassware, syringe, and needle must be clean, the vein must be entered by "primary intention," the blood must flow freely into the syringe with minimal frothing, the blood-filled clotting-time tubes must not be agitated, and the test must be completed promptly at the bedside.

There is no getting away from such stringent technical requirements, with either heparin or the coumarin drugs.

12. Q. Can the Whole Blood Clotting Time Be Used Instead of the Prothrombin Time As a Guide to Coumarin Therapy?
A. No. For heparin, the clotting time is invaluable as a guide. It is also useful in screening patients for a hemorrhagic diathesis, because an elevated clotting time indicates a profound coagulation disturbance. It should be emphasized, however, that many a serious defect can be masked by a normal clotting time. This is particularly true of "hypoprothrombinemic" states. Here the glass clotting time is most often normal despite marked depression of the coumarin-vulnerable clotting factors to a degree sufficient to cause bleeding. Under these circumstances the prothrombin time can be markedly elevated despite a normal glass clotting time. Although the clotting time in siliccone-coated tubes will be distinctly prolonged by coumarin therapy, the test under these conditions requires a long interval of observation by the technician and meticulous attention to technical details. For these reasons the prothrombin time determination is preferred as the guide to the use of coumarin drugs.

13. Q. As a Guide to Heparin, Is the Determination of the Clotting Time by the Capillary Tube Method As Satisfactory As Venous Blood in Regular Size Clotting-Time Tubes?
A. There is general agreement that the capillary tube method is unreliable, and therefore should not be used.

14. Q. Are There Any Tests Besides the Prothrombin Time Which Should Be Periodically Performed on a Patient Who Is on Long-Term Coumarin Therapy?
A. Although the prothrombin determination is the cardinal laboratory guide to coumarin therapy, it is known that bleeding may occur in some individuals despite maintenance of the prothrombic activity at levels considered compatible with normal hemostasis. The reason for this is obscure; it is probably attributable to factors outside of blood clotting that play important roles in the over-all hemostatic mechanism, or to the fact that some other clotting factor is affected which is not measured by the prothrombin assay. Accordingly, other tests are valuable. The hemoglobin level, as well as examination of the urinary sediment and stool for occult blood, should be determined periodically.

15. Q. Do the Anticoagulants Affect Important Laboratory Tests Such as Measurements of the Formed Elements of the Blood, Sedimentation Rate, Electrocardiogram, or Agglutination Tests?
A. As far as is known neither heparin nor coumarin derivatives significantly alter the parameters referred to. Heparin does, however, bind complement, and thus may interfere with certain serologic tests. Also, heparin is said to increase the resistance of red cells to hypotonic salt solutions.

16. Q. What Procedure Should Be Followed in a Patient on Long-Term Coumarin Therapy Who Needs Minor Surgery Such as Extraction of a Tooth or Removal of a Wart?
A. If the procedure is elective and can be delayed for several days, the anticoagulant should be discontinued, the prothrombin time determined daily, and the procedure performed when the prothrombin activity rises above 30 per cent. It is generally agreed that inordinate bleeding will not occur at or above this level. Therapy can be resumed on the day of surgery and followed daily until "therapeutic" levels are again obtained. If the procedure cannot be delayed, the administration of a small dose of vitamin K₃ (5 mg.) will hasten the return of prothrombic activity. In any event, the procedure should be done only after the pro-
thrombin determination indicates that it is safe to proceed. It should be mentioned, however, that some investigators believe that these minor procedures can be performed safely at the "therapeutic" range of prothrombic activity.

17. Q. Does the Same Hold True for Major Surgery?
A. The same considerations hold here also. If the procedure is elective, the patient can be properly prepared by postponing the operation for several days until the prothrombic activity rises above 30 per cent. If, on the other hand, the procedure is of an emergency nature, prompt correction of the drug-induced defect can be achieved by transfusion with blood or plasma, supplemented by intravenous vitamin K₁ (25 to 50 mg.). Since the clotting factors involved are relatively stable, it is not necessary that the blood be fresh; ordinary bank blood or plasma is adequate. The amount administered should be sufficient to assure a prothrombic activity of at least 30 per cent. In an average adult, 3 or 4 units of blood or plasma are likely to be necessary. Moreover, since it is possible that substantial blood loss may occur during the operative procedure, thus depriving the patient of prothrombin and the other clotting factors, additional quantities of blood or plasma should be readily available, and used during and following surgery, as indicated by clinical and laboratory observations.

Also of considerable value is the local use by the surgeon of topical thrombin applied liberally to oozing surfaces should undue bleeding be encountered.

As to resumption of anticoagulant therapy, the same procedure can be followed with major, as with minor, surgery with certain exceptions. Special caution is indicated in surgery involving lung, prostate, biliary tract, and extensive raw surfaces.

An alternative approach is feasible: the physician may choose to shift from coumarin to heparin therapy.

18. Q. How Long Must One Wait after Eye or Brain Surgery before Anticoagulant Therapy Can Be Resumed?
A. Although the general principles outlined in questions 16 and 17 regarding the reinstatement of therapy after surgery in general will also apply here, it is advisable to wait longer in eye or brain surgery because minor bleeding, which would be of little significance in other parts of the body, may have dire consequences in these organs.

A. Since the anticoagulant action of heparin is relatively transient, a lapse of 3 or 4 hours following the last dose (assuming it was administered intravenously) is sufficient protection against hemorrhage. This should be confirmed by a clotting time determination prior to operation. If surgery cannot be deferred for several hours, protamine sulfate should be administered (see p. 127). Other agents, such as toluidine blue or neutral red, are also effective, but blood and plasma have no antiheparin effect.

Clinical experience indicates that heparin can be resumed safely 24 hours or, on occasion, even immediately after surgery. Under special circumstances such as in vascular or cardiac surgery, heparinization may be advisable throughout the procedure. Conversely, any anticoagulant therapy following ocular or central nervous system surgery is distinctly hazardous and generally contraindicated.

20. Q. Do the Anticoagulants Affect Menstruation?
A. Frequently menstrual flow is increased and prolonged. This is of little clinical significance unless there is disease of the reproductive tract such as fibroids or cervical ulceration. However, drug-induced, excessive menstrual flow may eventually cause anemia from chronic blood loss, especially in long-term therapy. This can be treated by supplements of iron or by blood transfusions.

21. Q. How Do You Handle a Hemorrhagic Complication in a Patient on Long-Term Anticoagulant Therapy, in Whom You Would Like to Resume Therapy after the Bleeding Is Controlled?
A. The patient should be informed prior to treatment of the possibility of bleeding from the nose, gums, mouth, and vagina as well as into the urine, stool, and skin. The patient should always carry with him vitamin K₁ tablets (Mephyton) of 5 mg. each. The individual should promptly notify the doctor of any bleeding. The physician can then decide on the appropriate course of action: discontinuance of the drug, the immediate use of the antidote and in what amounts, or the use of hospital facilities for the appropriate laboratory studies or the administration of blood, plasma, or intravenous anticoagulants. When bleeding has stopped, anticoagulant therapy can be resumed, guided again by the usual laboratory determinations.

The physician must always be alert, furthermore, to the possibility of bleeding arising from other pathology.

22. Q. Are There Any Special Recommendations Concerning Records to Be Kept by the Patient or By the Physician?
A. The patient should not only be informed

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*In patients with limited cardiac reserve such volumes may be dangerous.
as to the general effects, nature, name, dose, and strength of the medication he is receiving, but should carry a card stating that he is on therapy, the drug and dose that he is taking, and that it may predispose him to undue bleeding in the event of accident. For the physician, a simple record form designed specifically for recording anticoagulant data will be found useful.

23. Q. Is There Any Food with Anticoagulant Properties?
A. For cattle, yes (spoiled sweet clover); for man, no.

24. Q. Besides Those Foods That Are Rich in Vitamin K, are There Any That Make the Blood Hypercoagulable? What is the Role of Fats in Clotting?
A. The vitamin K₁-rich foods have already been referred to (p. 128). There is only suggestive evidence that other foods have clot-promoting properties. The role of dietary lipids in coagulation is still obscure. Many observers report that after a fatty meal, in hyperlipemic states or following the addition of lipid material to blood in vitro, clotting is in some respects accelerated. The relevance of these observations to intravascular coagulation, however, is unresolved, and therefore, at present, the dietary management of patients should be predicated on other factors besides the possible effect on clotting.

25. Q. Is It True That Salicylates Have a "Prothrombinopenic" Effect? If So, Does This Preclude the Use of All Salicylates in Patients Receiving Coumarin-Type Drugs?
A. Salicylates in large doses are mildly "prothrombinopenic." On the other hand, "hypoprothrombinemia" of clinically significant degree is not observed even in those patients taking large amounts of salicylates for rheumatic fever or arthritis. Nevertheless, in view of the tendency toward gastric bleeding occasionally encountered in patients on salicylates, presumably attributable to local gastric irritation, it would seem wise to limit or omit salicylates in patients on anticoagulant therapy.

26. Q. Besides Salicylates, Are There Any Other Commonly Used Drugs That Influence Coumarin Therapy?
A. The question of antibiotics, already alluded to (p. 129) is significant in that they can enhance the action of coumarin derivatives by decreasing the supply of vitamin K₁ available from intestinal bacterial biosynthesis. With regard to steroids there is considerable experimental evidence that they increase the sensitivity of animals to the "prothrombinopenic" effects of these drugs, as well as the incidence of hemorrhagic complications. These observations do not, however, necessarily preclude coumarin therapy, but rather focus atten-

tion again on the importance of individualization of therapy.

27. Q. Are There Any Drugs That Accelerate Intravascular Coagulation?
A. The acceleration of clotting by stress and epinephrine has been known since the early work of Cannon and others. It has also been observed that in isolated clotting systems some commonly used drugs, such as digitalis, mercurial diuretics, and benadryl may accelerate clotting kinetics. As yet there is no clear-cut evidence that these effects are clinically significant. Recently, chlorpromazine and reserpine have been implicated in causing thrombosis, although the actual underlying mechanisms are unknown. As the question implies, the physician should remain alert to the possibility that these and other commonly used therapeutic agents may actually precipitate or aggravate intravascular coagulation.

28. Q. How Should Heparin Be Administered?
A. Heparin may be administered intravenously by constant infusion, by intermittent injections on schedules ranging from every 2 to 8 hours, and by the intramuscular and subcutaneous routes in a variety of menstrums. Based on control of the antithrombotic effect, reliability, safety, and unpleasant side reactions, the intravenous route on 4 or 2 hourly schedule is at least as satisfactory, if not superior, to any other regimen. Intravenous administration will be facilitated by the use of an indwelling plastic catheter inserted into a superficial forearm vein. Daily examination of these catheters will minimize the risk of sepsis involved in their use. The initial dose requirement is usually 50 to 75 mg.; subsequent individual doses to be injected (25 to 125 mg.) are determined by the clotting time. The dose selected should be so calculated as to induce, 4 hours after its injection, a clotting time of approximately twice that of the pretreatment value. After this dose requirement has been established, the clotting time should be determined once daily 4 hours after the last dose to exclude a possible increase in the anticoagulant effect of the drug and to allow for variations in heparin requirements during the course of treatment. In contrast to the coumarins, laboratory tests guiding heparin therapy do not require special reagents or a highly trained technician.

29. Q. Many Believe That Heparin Is Just As Effective When Administered Subcutaneously As When Given Intravenously. Would It Not Be Distinctly Advantageous to Use the Subcutaneous Route Rather Than the Intravenous If the Former Is Satisfactory? Why Is There This Difference of Opinion?
A. In contrast to intravenous administration, the subcutaneous route occasionally results in a
ANTICOAGULANT THERAPY

more erratic clotting time elevation. Also, local pain, ecchymoses, and rarely neuritis may occur at the injection site. This may be compounded if other medications are also being administered by this route. Moreover, reversing the anticoagulant effect with protamine, should this be necessary, is more difficult after subcutaneous than after intravenous administration (see p. 127). Finally shifting from heparin to coumarin-type agents is less difficult when the route of heparin administration is intravenous. For these reasons the intravenous route is considered preferable, although it is recognized that satisfactory elevations of the clotting time may be obtained by the subcutaneous or intramuscular administration of heparin. New heparin preparations for subcutaneous use are currently under investigation.

At present heparin can effectively be administered intravenously for several weeks.

30. Q. Are There Situations Where Heparin Is Preferable to Coumarin-Type Compounds? How Should a Patient Be Changed from Heparin to a Coumarin?

A. Heparin is the drug of choice for emergency situations in which immediate therapy is indicated. Other circumstances where this agent has advantages over the coumarins are discussed in the text. In addition, heparin is generally more advantageous when laboratory facilities are limited. When the physician contemplates shifting to coumarin drugs after initiating treatment with heparin, both agents are given initially until the full anticoagulant effect of the coumarin becomes manifest. Some observers believe that heparin can then be discontinued (i.e., 1 or 2 days after the beginning of coumarin therapy), whereas others believe that heparin should be continued for another 4 to 6 days after the anticoagulant effect of the coumarin drug has become apparent. In either event, the dose of each agent should be regulated by the appropriate laboratory guide. It should be recognized that the coumarin agent, although it does not interfere with the clotting time determination, may make the patient more sensitive to heparin. Furthermore, the ability of heparin to affect the prothrombin time determination requires that the clotting time is not affected by heparin (4 or more hours after its administration). This specific problem is difficult to overcome if the patient is receiving heparin by either subcutaneous or intramuscular routes because the sustained elevation of the clotting time indicates continued heparin effect which interferes with the accuracy of the prothrombin determination.

31. Q. What Is the So-Called "Rebound Phenomenon"?

A. There is an impression, held by many observers, that following the abrupt discontinuance of anticoagulant therapy, there is a significant incidence of recurrent thrombosis. It has also been observed that certain clotting factors may attain abnormally high levels after cessation of coumarin therapy. It has also been observed that discontinuing heparin may result in an abnormally shortened clotting time. These elevations following cessation of coumarin therapy are said to be even more pronounced if the termination of therapy is hastened by the administration of vitamin K1. This has been interpreted as a "rebound" effect. Whether this phenomenon is the cause of the observed recurrent thrombosis is unknown. Nevertheless, these impressions and observations provide sufficient basis for the recommendation that both heparin and coumarin be discontinued gradually rather than abruptly, and that the use of vitamin K1 in stopping therapy be avoided where possible.

32. Q. Are There Any Laboratory Tests for "Hypercoagulability"?

A. A variety of in vitro coagulation abnormalities has been observed in patients with thrombotic tendencies. These include the increased resistance of the patient's blood to the clot-retarding effects of heparin added to blood in vitro (the heparin-tolerance test); elevated levels of factors I, VII, and X; accelerated generation of intrinsic thromboplastin; faster than normal prothrombin time; shortened glass and silicone clotting times; and increased platelet stickiness. These abnormalities, however, do not correlate sufficiently with intravascular coagulation to permit their acceptance as in vitro assays of thrombosis. Accordingly, there is at present no reliable test to indicate the impending, incipient, or actual thrombotic state.

33. Q. Is There an Age Limit to the Use of Anticoagulants?

A. Here again one can be too arbitrary. There is little question that in advancing years obstacles arise that make therapy more difficult, if not hazardous. Older patients are apt to be forgetful and uncooperative, they may have a faulty hemostatic mechanism by virtue of loss of skin elasticity and greater fragility of blood vessels (purpura senilis). Renal function is apt to be compromised, and dietary irregularities are fairly common in older individuals. On the other hand, the usually accepted indications for employing anticoagulants become more common. Age per se should not impose limitations on the use of anticoagulant drugs.

Summary

The physician who undertakes anticoagulant therapy tampers with one of the most important homeostatic functions of the body. In so doing, he subjects the patient to the
calculated hazard of possible hemorrhage balanced against the risks of the thrombosis or embolism that he seeks to prevent or treat. Agents currently employed are heparin and coumarin-type compounds. These two categories of anticoagulants act at different sites of the coagulation mechanism, are administered differently, are metabolized differently, are reversed by different antidotes, and their effects are measured by different tests.

Certain facts about which the physician should be adequately informed have been presented regarding the hemostatic mechanism; the physiology and pharmacology of the anticoagulants, especially as they may explain the wide variation in individual response; certain aspects of methodology; and the various practical problems involved in therapeutic management. Emphasis has been placed on the importance of individualization of treatment, careful clinical observation, and frequent reliable laboratory tests as guides to proper therapy.

Selected References

Varying results depend on the greater or less diminution of the volume of air usually contained in the thorax (lungs); and the cause which occasions this diminution, whether solid or liquid, produces analogous results to those obtained by striking a cask, for example, in different degrees of emptiness or fulness: the diminution of sound being proportioned to the diminution of the volume of air contained in it.—From On Percussion of the Chest. Published in 1761. Translated by John Forbes, M.D. In: Classics of Medicine and Surgery. New York, Dover Publications, Inc., 1959, p. 128.
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