The George E. Brown Memorial Lecture

Current Status of the Problem of Thrombosis

By Nelson W. Barker, M.D.

The pathogenesis of intravascular thrombosis involves 1 or a combination of 3 factors: an endothelial lesion, a disturbance of blood flow, and hypercoagulability of the blood. The fate of fresh thrombi is probably dependent on the fibrinolytic activity of the plasma. While some tests for coagulation factors have given some positive results among patients with various types of thrombosis, no test has consistently demonstrated its value in predicting a thrombosing tendency. Carefully administered anticoagulant therapy has been effective in the prevention of thrombosis in many patients. Such therapy requires individualization on the basis of frequent laboratory tests and is usually justified only after the patient has suffered one or more episodes of clinical thrombosis. Treatment of acute thrombosis by intravascular injections of fibrinolytics is still in the experimental stage. Recent advances in surgical technic have led to successful restoration of continuity of some of the large arteries previously occluded by thrombosis.

In spite of expanded anticoagulant therapy, new antihypertensive drugs, controversial anti-atherogenic regimens, and spectacular cardiovascular surgical treatment, it is apparent that we have not really solved the problem of thrombosis. It has been emphasized repeatedly that cardiovascular diseases are the most common cause of death at the present time. In the majority of cardiovascular deaths, the terminal event can be attributed to intravascular thrombosis. Necropsy evidence indicates that although atherosclerosis is the basic disease, final arterial occlusion by thrombosis is responsible for approximately 80 per cent of transmural myocardial infarctions. Similar evidence indicates that regional arterial thrombosis is responsible for 50 to 80 per cent of infarctions of the brain. Some cerebral and coronary occlusions, as well as arterial occlusions in many parts of the body, are caused by embolic detachments from thrombi formed in the heart itself. Patients still die of pulmonary embolism that starts as thrombosis in the peripheral veins. In addition to the lethal aspects of thrombosis, it is the cause of much serious disability from nonfatal cerebral and myocardial infarction and from thrombotic occlusion of peripheral arteries and veins causing serious circulatory insufficiency and, at times, loss of digits or limbs. It is well recognized that arterial thrombosis is usually a complication of a disease process in the vessel walls themselves, most commonly atherosclerosis. If thrombosis could be prevented, the seriousness of athero-sclerosis would be greatly reduced. Also if all thrombosis could be prevented, a considerable number of other deaths and instances of serious disability due to nonatherosclerotic thromboembolic diseases could be eliminated.

Etiologic and Pathogenic Aspects

It is obvious that to consider thrombosis as a single pathologic and etiologic entity is an oversimplification of a very complex problem. For example, we see thrombosis developing in individuals only when there is serious and advanced disease of the wall of the blood vessel at the site where the thrombus is formed. We see other instances in which no definitive pathologic process can be seen in the vessel wall in or near where the thrombus develops, and we see all sorts of cases between these two extremes in which there is some combination of vascular disease and thrombotic occlusion. It is interesting to note that

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our knowledge concerning the etiology and pathogenesis of intravascular thrombosis has progressed very little during the past 50 years since Welch\(^1\) wrote his classic chapter on the subject about the turn of the century. It is still generally accepted that thrombosis develops as a result of one or more of the following factors: cardiovascular endothelial disease or injury, relative stasis or impairment of regional blood flow, and increased coagulability of the blood.

**Endothelial Disease and Injury.** The tendency for thrombosis to occur in vessels affected by atherosclerosis or chronic inflammatory disease is well known. Thrombosis also occurs on the endothelial side of myocardial infarcts, on the stretched and damaged lining of arterial aneurysms, and in veins at the site of chemical or mechanical injury.

**Slowing of Venous Blood Flow.** Many cases of venous thrombosis are associated with slowing of venous blood flow as the result of rest in bed and pressure on the veins of the lower limbs in patients who cannot or do not move or change their positions frequently. Alterations in blood flow in arterial aneurysms, in fibrillating atria of the heart, and in varicose veins of the extremities are considered to be important factors in the thrombosis that frequently develops in these locations.

Recently studies\(^2\) have been reported on the flow of liquids through artificial tubular systems to show the variations of marginal flow where the channels were tortuous, angulated, or of varying caliber. Flow of certain solutions through such tubes resulted in slow depositions on the sides of the tubes where the flow was slower. By analogy a gradual deposition of fibrin and formed elements of the blood may occur in tortuous vessels, in those of varying caliber, and near the orifices of small branches of larger vessels.

**Hypercoagulability of Blood.** It is presumed that hypercoagulability of the blood is a factor in many cases of intravascular thrombosis. However, attempts to establish a consistent measurable disturbance of coagulation in patients with recent thrombosis have not been successful. Many such tests have been studied, several of which have shown some tendency toward positive results in patients with thrombosis as compared with normal persons. However, overlapping values above and below any selected upper limit of normal, in both the tested and the control subjects, have weakened the significance of each test. Among some patients with thrombosing tendencies the concentration of fibrinogen in the blood is relatively high, but, when tests of fibrinogen are done on a sufficient number of persons at varying times, it is found that the variations in the level of fibrinogen among different persons as well as in the same persons at different times are so great that only a few patients with thrombosis can be said to have abnormal concentrations of fibrinogen.

Tests of prothrombin activity for either prothrombin itself or the stable and labile accelerators, or the combination of all, have not yielded distinguishable results in patients with thrombosis.\(^3\) The same can be said for tests of antithrombic activity. The coagulation time of whole blood in glass tubes is not shortened in patients with thrombosis except in an occasional person. Furthermore, the significance of such tests is impaired because of variability of results that occur because of minor and often unavoidable variations in technic. When the clotting test of whole blood is done in silicone tubes and the preparation kept at a temperature of 37°C, and when considerable attention is paid to consistency in technic, a greater number of patients show more rapid coagulation of blood than the normal range, but there is still considerable overlap in values when normal persons are compared with those who have thrombosis.\(^4\) An even larger percentage of positive results has been obtained with the heparin tolerance test\(^5\) and with the test done by determining the coagulation time in a glass tube at 37°C of a mixture of a fixed amount of heparin and a fixed amount of whole blood made immediately after withdrawal of the blood from a vein.\(^6\) In one such series of tests, when an arbitrary time was used as the low limit of normal, it was found that 20 per cent of
normal persons and 80 per cent of patients with thrombosis had heparin coagulation times shorter than normal.

Much attention has been paid to the possible role of abnormalities of thrombocytes as a cause of thrombosis or a tendency to thrombosis. Although there seems to be some tendency for thrombosis to develop in patients with high platelet counts, most patients with thrombosis have normal platelet counts. Studies of variations in morphology and degree of clumping of platelets in stained smears have shown only occasional abnormalities of questionable significance in patients with thrombosis. Attempts to study platelet function have encountered technical difficulties. Some studies of platelet adhesiveness to glass have indicated a greater tendency to such adhesiveness among some patients with thrombosis, but such tests are time-consuming and often give inconsistent results. The test of thromboplastin generation has produced a few positive results in patients who have had repeated thrombotic episodes. The test is technically difficult and time-consuming but deserves further appraisal and, if possible, simplification. One study seemed to indicate a significantly shortened clot retraction time in many patients with pulmonary embolism and a somewhat shortened clot retraction time in patients with thrombophlebitis, but these results have lacked confirmation. The test is relatively simple. Positive results might be attributed to a change in platelet function. The available evidence, although meager and perhaps controversial, would seem to indicate that if a coagulation defect does exist in patients who have thrombosis, it is probably in the first stage of coagulation and associated with platelet function or the ease with which plasma thromboplastin is formed. Conflicting reports have appeared in the literature regarding shortening of the coagulation time of whole blood in lusteroid and silicone-coated tubes after ingestion of a fatty meal. It has also been reported that ingestion of a fatty meal inhibits fibrinolytic activity of the plasma. The studies were all done in normal persons. Even if some hypercoagulability or inhibition of endogenous fibrinolysis occurs regularly after ingestion of fat in almost all people, the significance of these changes in the development of intravascular thrombosis has not as yet been demonstrated.

Clinical Observation Related to Pathogenesis. In the consideration of the pathogenesis of thrombosis, there are some curious clinical observations that must be taken into account in efforts to elucidate the mechanism. One of these is the fact that thrombosis may develop at an interval, for example 7 to 14 days, after tissue trauma and blood loss. A second observation is that thrombosis tends to be episodic, and a third is that for some curious reason thrombosis fails to progress beyond a certain limit. It is not easy to understand why it does not continue to progress, once it has started. Another observation is that even when patients have conditions that are known to be complicated by venous thrombosis the actual incidence of this complication is small. This applies, for example, to patients who have postoperative thrombosis, postpartum thrombosis, posttraumatic thrombosis, or thrombosis occurring as a complication of severe infectious diseases.

These observations would suggest that a combination of etiologic factors may be necessary for the development of thrombosis and that at least one of the factors may be transitory. They might also suggest that an increased amount of some one of the factors promoting blood clotting is present at the time of thrombosis, but may be used up during the process of thrombus formation, therefore limiting the extent and progression of the process. Conceivably this might account for the fact that measurable changes in coagulation factors have been found only inconsistently after thrombosis has occurred. The possibility that a measurable disturbance of coagulability of the blood may be present just before an episode of thrombosis has not been sufficiently explored. Because many of the tests of blood coagulation that have been tried in an effort to determine the presence of a clotting or thrombosing tendency have been time-consuming and subject to technical error,
satisfactory appraisal of the value of the tests has been limited.

**Spontaneous Thrombolysis.** Some information is available and more is needed on the changes that occur in thrombi after they are formed. There is a tendency to think of thrombosis as a static process, that once it has occurred the vessel is occluded by the thrombus permanently and that the thrombus remains as such. However, clinical, pathologic, and experimental evidence indicates that parts or all of many thrombi disappear as a result of endogenous fibrinolysis. The fate of many thrombi is partial lysis and partial fibrous tissue organization. This is the usual end-stage of iliofemoral thrombophlebitis. The marginal organization produces thickening of the wall of the vein that results in reduction of the lumen of the vein and crippling of the valves, but a lumen still remains patent and functioning. Many thrombi in other parts of the body, both in arteries and veins, undergo at least partial lysis within hours or days after they have been formed. In animals the production of thrombi in veins by means other than severe endothelial injury is almost always followed by disappearance of the thrombi in a matter of a few hours.

In the syndrome of insufficiency of the basilar artery, the clinical course is characterized by repeated episodes of transient cerebral dysfunction that last only a few minutes or hours. These have been attributed by some to arterial spasm or to alteration in the blood flow through narrowed atherosclerotic arteries. However, in many cases adequate anticoagulant therapy has promptly stopped the recurrence of the episodes. There is no evidence that the anticoagulant therapy has anything to do with blood flow or arterial spasm, and its only known action is the prevention of fibrin formation. Thus it is more logical to assume that the episodes of cerebral dysfunction are produced by transient arterial thrombosis which may be prevented by the anticoagulant. If so, the thrombotic occlusions must be transient and must disappear spontaneously in a few minutes or hours. If we accept the concept that in normal persons there is continuous deposition of a small amount of fibrin on the vascular endothelium and continuous lysis of this fibrin, a small alteration in this homeostatic balance may be responsible for the development of thrombosis in some situations. Another small alteration may produce rapid lysis of a freshly formed thrombus. Much work has been done in an attempt to evaluate the action of the fibrinolysis of the blood plasma. The evidence indicates that a homeostatic situation is normally present in which the fibrinolysins in the plasma are balanced by antifibrinolysins. Thus, some of the principles that are important in both the development and involution of thrombi may be related to this homeostatic fibrinolysin-antifibrinolysin balance.

**Preventive Therapy**

In spite of the limitations of knowledge concerning pathogenesis and etiology, some progress has been made in the treatment of thrombosis and particularly in the prevention of thrombosis. There is little doubt that early ambulation after surgical operation and childbirth has lessened the incidence of venous thrombosis and pulmonary embolism that may occur in the immediate postoperative and postpartum convalescence. However, early ambulation has not eliminated thrombosis under these conditions. After extensive surgical procedures, or when other complications exist, many patients cannot be ambulated early or will not ambulate to a degree that will eliminate or reduce the postoperative venous stasis in the lower extremities. Obviously, many patients who have had fractures, or who have had orthopedic operations, cannot be ambulated for several weeks. The value of elastic stockings or of elastic bandages on the legs during the immediate postoperative period is doubtful. Perhaps the failure of such supports is due more to their application than to the principle involved, but for purposes of eliminating venous stasis in the lower extremities it is probable that the use of supports is much inferior to adequate exercise of the leg muscles.

The most common and important cause of intra-arterial thrombosis is the endothelial disease produced by atherosclerosis. It is prob-
able that if atherosclerosis could be prevented, or could be arrested in its early stages, most of the killing or crippling thrombosis that occurs in the heart and brain could be prevented. In spite of an extensive program of research, which is currently almost worldwide and involves many disciplines, the solution of this problem seems to be still rather remote.

Anticoagulant Therapy. The greatest advance in the prevention of thrombosis, whether intravenous, intra-arterial, or intracardiac, that has occurred to date has been anticoagulant therapy. In spite of the calculated risks of this therapeutic approach, the necessity for careful individualization of programs for each patient, the numerous blood tests that are required, and the occasional contraindications and occasional failures, the use of anticoagulants for the prevention of thrombosis in many different locations in the body has been gradually extended. There is adequate evidence that anticoagulant therapy is effective in the prevention of most venous thrombosis and pulmonary embolism,\(^{16}\) that it has greatly reduced the incidence of thromboembolic complications and that it has significantly lowered the mortality rate following acute myocardial infarction.\(^{17}\)

More recently, there is statistical evidence that adequate anticoagulant therapy carried out on a long-term basis in patients who have had one or more myocardial infarctions and survived has significantly reduced the subsequent death rate.\(^{18}\) Also there is recent evidence that thrombosis of the basilar artery can be prevented by adequate anticoagulant therapy and that such therapy is probably also effective in the prevention of thrombosis in the carotid arterial systems.\(^{19}\) Anticoagulant therapy is being used, apparently effectively, in several other situations in which specific statistical information is lacking as to its effectiveness. These include acute peripheral thrombotic and embolic arterial occlusions,\(^{20}\) recurrent peripheral arterial thrombosis, and recurrent idiopathic thrombophlebitis.

It has been stated repeatedly that the purpose of anticoagulant therapy is to prevent thrombosis by partially interfering with the coagulability of the blood and that anticoagulant therapy has no effect on thrombi or emboli that are already in existence when the therapy is started. This of course presumes that thrombosis is a static process and does not take into consideration the possible interrelations between fibrin formation and fibrinolysis. One well-controlled study of experimental thrombosis in the arteries of animals indicated that lysis of the thrombi and restoration of the lumen of the arteries was much more rapid and more nearly complete when anticoagulants were given soon after the thrombi were produced than when they were not so given.\(^{21}\) It is a common clinical impression that the signs and symptoms of acute peripheral arterial and venous thrombosis disappear more rapidly when anticoagulants are used. Theoretically at least, the inhibition of fibrin formation by anticoagulants may permit spontaneous fibrinolysis to occur more rapidly and to a greater extent than it would occur otherwise.

Anticoagulant Drugs. The anticoagulants in current use are heparin, several coumarin compounds, and phenindione. Although less commonly used, heparin is still a satisfactory anticoagulant and one for which there is no substitute from the standpoint of rapidity of action. The necessity for parenteral administration makes it unsuitable for long-term anticoagulant therapy. Attempts to develop other satisfactory anticoagulants having a heparin-like action have not been successful to date. Clinical studies with 2 of these, Paritol and Treburon, were abandoned because of toxic reactions which have not occurred with the use of heparin. Dextran has not been used sufficiently to evaluate properly its possible toxic effects.

Most of the anticoagulant therapy that is used currently employs one of the coumarin compounds or phenindione. Heparin may be used to cover the initial period between the beginning of treatment and the time when therapeutic hypoprothrombinemia is achieved. Dicumarol is still used widely and preferred by many clinicians because of their long experience with it. Several other coumarin com-
pounds and phenindione have been developed as substitutes for Dicumarol in an effort to lessen or eliminate some of its disadvantages, namely the delayed onset of its action, the persistence of its effect for several days after administration is discontinued, and the rather wide variation of response among different patients. The medical literature would seem to indicate that there is some disagreement as to which of the available coumarin compounds is superior. Actually the differences in action, for example, between Dicumarol, Tromexan, warfarin sodium and phenindione, which are the drugs chiefly used for this purpose in this country today, are so slight that it is probable that the choice is largely a matter of experience of the individual physician. In the hands of an experienced clinician, satisfactory results may be obtained with any of these drugs; and if therapeutic hypoprothrombinemia is established and maintained by any of them, it is almost certain that the same degree of antithrombotic action will be obtained and there will be the same risk of bleeding in an individual patient as would prevail if any other of these drugs were used. Of these compounds, only warfarin sodium is sufficiently soluble so that a neutral solution may be administered intravenously or intramuscularly. Theoretically, warfarin sodium is better absorbed than the others through the gastrointestinal tract, and should have a more predictable effect. Practically, however, so many other factors influence the response of the particular patient to a certain dose of one of these compounds that there is little advantage in giving warfarin sodium over the other compounds unless it is desirable to give the anticoagulant parenterally, because of vomiting or some gastrointestinal defect.

Prothrombin Time. It should still be emphasized repeatedly that the coumarin compounds and phenindione should never be administered unless the 1-stage determination of prothrombin time can be made repeatedly to check the effect of the drug and to guide the future dosage. It should also be emphasized that in each patient the regulation of dosage is an individualized affair, depending upon the response as indicated by the results of the test. If the prothrombin time is kept within the therapeutic range, the danger of bleeding, which is the only serious complication of this type of therapy, is minimal. Most instances of serious bleeding occur when the prothrombin time, either inadvertently or through negligence, exceeds the therapeutic range. However, it must be remembered that bleeding may occur occasionally even when the prothrombin time is within the therapeutic range if the patient has a potentially bleeding lesion. For purposes of stopping the anticoagulant action of the coumarin and indandione compounds, vitamin K₁ is now commercially available. Its effect is not immediate but after its use the prothrombin time almost always falls in a matter of a few hours and it is the most valuable antagonist for bringing the prothrombin activity back to normal as rapidly as possible. In some instances, transfusion of blood may be indicated to replace blood loss, but such transfusions have only slight or temporary effect in lowering the prothrombin time.

In situations in which vitamin K₁ is indicated at all, the amount that will be necessary to bring the prothrombin time back to normal as rapidly as possible is unknown. While a dose of 50 mg. may be sufficient for many patients, it will not be sufficient for all patients, and it is advisable in a serious and critical situation, where bleeding has developed, to give at least 250 mg. either orally or intravenously. A theoretical objection to a large dose of vitamin K₁ is that this not only may restore the prothrombin time to normal, but also may make the blood more coagulable than it was prior to administration of the anticoagulant. However, no tests have indicated that such hypercoagulability is produced by vitamin K₁ in doses as large as 500 mg. and I do not believe that such hypercoagulability ever occurs.

The importance of the 1-stage determination of prothrombin time as a guide to therapy with the coumarin and indandione compounds has been repeatedly emphasized. It is probable that this test is not an accurate measure of either the antithrombotic or the potential bleeding effects of these anticoagulants.
ever, many years of experience by many persons has demonstrated that it is a good practical measure of such effects. The test itself is simple and, although there is difference of opinion as to the best type of thromboplastin, the major reagent to be used in the test, and there is great necessity for the laboratory personnel to have experience with the thromboplastin that they use and to prepare it carefully so that the results of the test are reproducible from day to day, accurate tests are being performed with good day-to-day reproducibility not only in large medical centers in large cities throughout the country, but also in many small hospitals and small communities.

Since the 1-stage determination of prothrombin time was first recommended as a guide to the dosage of Dicumarol, many attempts have been made to develop a simpler and more accurate test. To date I do not think such a test has been developed and any test for this purpose will require prolonged usage in many patients before it can be truly evaluated. A recent report has stated that coumarin therapy could be controlled satisfactorily and simply by determination of the coagulation time of whole blood. I would like to sound a warning against substituting this test for the 1-stage determination of prothrombin time. In the first place, determination of the coagulation time of whole blood is subject to many errors and the results can be varied by small differences in technic. Even when the test is done carefully, if there is significant prolongation of the coagulation time it usually means that the effect of the anticoagulant has exceeded the therapeutic range as indicated by the 1-stage determination of prothrombin time. Therefore, if the coagulation time of whole blood is used as a guide, the danger of bleeding will be increased.

Admittedly, anticoagulant therapy with the coumarin compounds, with its implied necessity for multiple determinations of prothrombin time and the need for careful individualization of dosage schedules for each patient, has always been somewhat cumbersome and required time and experience on the part of the physician for the securing of optimal results. Admittedly also, there has always been a desire for a simpler and safer method of producing a similar type of anticoagulant effect. However, I doubt that, when the therapeutic principle of impairing blood coagulation is used to prevent thrombosis, it will ever be possible to simplify this type of treatment or to carry out such treatment without repeatedly checking the effect on the coagulability of the blood itself. Also, I doubt that any new coumarin or indandione compound or other drug having similar effect will be developed that will be superior and easier to administer than are the compounds that are available at the present time. This should not preclude the search for a better, simpler, and safer antithrombotic therapeutic principle.

**Other Therapeutic Considerations**

*Thrombolytic Agents.* Although the basic mechanical structure of most thrombi is more complicated than that of simple blood clots, the solidifying element in both is fibrin. Since fibrin is a mesh produced by polymerization of the cigar-shaped molecules of fibrinogen, and since it is well established now that certain enzymes (fibrinolysins) destroy this mesh, it is a logical step to try to destroy fresh thrombi in blood vessels by these fibrinolytic agents. It is known that a fibrinolysin (plasmin) is present normally in the circulating blood, but that under most conditions it is kept in an inactive state by the presence of an antifibrinolysin.

In recent years research has been carried out in an attempt to produce thrombolysis by the introduction of 3 different types of fibrinolysins into the blood stream. A basic problem in this therapeutic approach has been to get the fibrinolysin into the blood stream in sufficient concentration without producing toxic effects and to get it in actual contact with the thrombus. The use of dilute solutions of purified trypsin for this purpose has been at least temporarily abandoned because of toxicity and lack of demonstrable effectiveness in producing lysis of known and observable thrombi. Also, because trypsin may injure
the endothelium of blood vessels at the site of injection and produce increased coagulability of the blood, actual thrombosis has occurred at the site of its injection and in some instances for a considerable distance from this site. Fibrinolysins of bacterial origin, such as streptokinase, have had too much pyrogenic effect to be of any practical value. More recently, concentrates of plasmin, the naturally occurring fibrinolysin in human plasma, sometimes combined with small amounts of streptokinase, have been tried, but to date their use must still be considered strictly experimental and potentially hazardous. There is at least the theoretical hazard of proteolytic action on fibrinogen and other blood proteins, and there appears to be some risk of a refractory phase, after administration of the plasmin is stopped, in which there seems to be an increased tendency to progression of thrombosis. In spite of the difficulties and hazards of attempting therapeutic thrombolysis with fibrinolytic agents, continued research along these lines is highly desirable. It should be emphasized that thrombolytic effects can be expected only in relatively fresh thrombi, not more than a few days or certainly a few weeks old, since after this time the remainder of all thrombi that have not been spontaneously lysed have become organized by fibrous tissue.

Surgical Procedures. The great advances that have been made in the technics of vascular surgery during recent years have resulted in some brilliant successes in the treatment of localized thrombotic occlusion in large vessels. Ligation of large venous trunks proximal to the site of venous thrombi, for the purpose of preventing pulmonary embolism, is done much less frequently now than it was a few years ago. However, the successful removal of recent thrombi in iliofemoral veins without concomitant ligation of these veins has recently been reported. Segmental occlusion of the abdominal aorta and the iliac and femoral arteries by atherosclerosis and thrombosis has been attacked by several surgical technics, including thrombo-endarterectomy, segmental resection, and replacement by homograft or prosthetic tubes, and by-pass operations anastomosing homografts or prosthetic tubes above and below the obstructions without excision of the occluded segment. When one considers the tendency for blood to clot when exposed to a foreign surface, it is truly remarkable that thrombosis does not always occur in grafts or prostheses or in segments of arteries where thromboendarterectomy has been carried out. However, the number of instances in which successful operations are done and adequate circulation is restored without thrombosis in the graft, prosthesis or operated segment of artery is steadily increasing. Currently, operations of the type mentioned are not technically feasible for occluded segments in small arteries.

When operations of the type mentioned are contemplated, the risk of the operation and its chance of success should be carefully balanced against the expected benefit to the patient and the seriousness of the localized arterial obstruction. The successes that have attended this surgical approach to the problem of thrombosis in at least one of its phases and the steady advance in surgical technics give hope of an even greater expansion of this therapeutic approach for the future.

Summary

The medical profession, with much help from the basic sciences, has achieved some success in the attack on the problem of thrombosis. The therapeutic approaches are somewhat crude and much fundamental knowledge concerning the pathogenesis of this process is lacking. It is equally obvious that we have a long way to go to solve the problem. It is my opinion that further research is desirable in the detection of disturbances of blood coagulability that may lead to thrombosis and in the development of simplified tests that may be used to detect such tendencies. If by a test or series of tests of the blood an increased or imminent risk of thrombosis could be predicted, anticoagulant therapy could be used more effectively. The problem of the etiology and pathogenesis of atherosclerosis, which is the basis for most of the arterial thrombosis that we have to deal with, is being studied from many angles and by many com-
petent investigators. These researches should be continued and, if possible, expanded. The currently used programs of anticoagulant therapy should be extended and emphasis should be laid on careful individual supervision of such therapy. This implies the expansion of availability of accurate and consistent tests to determine the effect of the anticoagulants. The search should not be abandoned for other therapeutic agents that may correct hypercoagulability and thrombosing tendencies of the blood by a different action than that of the anticoagulant agents that are employed at the present time. Research should continue in attempts to develop a safe program and method for the use of fibrinolytic agents in the treatment of acute thrombotic processes. It is hoped that even further advances in vascular surgical technics will lead to increased safety and effectiveness of operations for the restoration of normal circulation where there has been thrombotic occlusion of segments of the vascular system. A combination of efforts in these directions plus the always present possibility of some previously unconsidered approach to the problem gives hope that thrombosis, the killer and disabler, may ultimately be brought under control.

SUMMARIO IN INTERLINGUA

Le profession medical—con multe auxilio ab le scientias fundamental—ha attingite un certe successo in su attacco contra le problema del thromboses. Le modos de terapia es satisse crude, e multe information de base in re le pathogenese del processo in question remane a discoperir. Il es obvie que le solution del problema non potte esser expectate in le proxime futuro. In mi opinion, recercas additional es desirabile in le detection de disturbationes del coagulabilitate sanguine que potte resutlar in thromboses e in le disveloppamento de simplificate tests que potte esser usate pro deteger tal tendentias. Si le uso de un test o de un serie de tests del sanguine potteva predicer un risce augmentate o imminente de thrombosis, le application de terapia anticoagulante devenirea plus efficace. Le problema del etiologia e del pathogenese de atherosclerosis (que es le base del majoritate del thromboses arterial que reclama nostre atten-
tion) se trova sub investigation ab multe punctos de vista e per multe expertos competente. Iste recercas debe esser continue et, in tanto que possibile, augmentate. Le currentemente usate programmas de terapia anticoagulante debe esser extendite con attention special prestate al meticuloase surveilantia individual del regime. Isto significa le desiderato de expander le disponibilitate de accurate e uniforme tests pro determinar le effecto del anticoagulantes. Al mesme tempo, on non debe abandonar le efforto de trovar altere agentes terapeutice que esserca capace a corriger hypercoagulabilitate e tendentias thrombotisante del sanguine per un action differente de illo del presentemente usate agentes anticoagulatori. Debe esser continua le recercas qu visa a disveloppar un innocente programma e methodologia pro le uso de agentes fibrinolytic in le tratamiento de acute processos thrombotic. Il es a sperar que progressos additional del technicas de chirurgia vascular va resulter an ancora plus alte grades de securitete e efficacia in le operaciones que restaura un circulation normal in casos in que segmentos del systema vascular ha suffrite un occlusion thrombotic. Un combination de effortios in iste directions—e le semper presente possibilitate del disco-perta de un previamente non considerate modo de attaccar le problema—va justificar nostre spero que thrombosis, causa de morte e de invaliditate, potte in fin esser fortitae in submission.

REFERENCES


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