Antiplatelet Aggregant Agents and Thrombolytic Compounds in Myocardial Infarction: Current Status

By Stanford Wessler, M.D., and Laurence A. Sherman, M.D.

ON MANY FRONTS, both prophylactic and therapeutic, major efforts have been or are about to be undertaken to decrease what some have termed the "epidemic" of coronary artery disease and acute myocardial infarction in our society. The difficulties confronting the clinical investigator who wishes to mount a meaningful therapeutic attack on this problem are great and stem from several sources.

Mortality Rate Variations. Institutional mortality rates vary from 10 to 45% among patients hospitalized with acute myocardial infarction. The therapy to be evaluated thus may be significantly affected by the nature of the population tested, as reflected by its mortality rate, and the results obtained may not be applicable to apparently comparable populations in adjacent hospitals or in institutions in other cities or countries. Such basic differences in populations are widened still further when investigators increase the selectivity of their study populations by establishing different diagnostic or other clinical criteria for the inclusion or exclusion from the study of patients purported to have acute myocardial infarction and by employing non-standard treatment criteria for complications such as arrhythmias and heart block.

Coronary Artery Occlusion. There is no agreement concerning the incidence of fresh coronary artery thrombosis in patients with acute myocardial infarction. Among autopsied cases the reported incidence ranges from 0 to 96%.1 However, in most series which exclude patients with angina and sudden death and in whom careful dissections are performed, fresh thrombi are reported in at least half and frequently in more than 75% of the autopsied cases.2,3 Acute myocardial infarction may result, without thrombotic occlusion, from fresh narrowing of the coronary arteries or from increased cardiac work, such as from physical exertion, anemia, or thyrotoxicosis, without any acute morphologic change in the coronary arteries. Furthermore, most coronary artery thrombi are primarily white on platelet lesions and only rarely develop red tails—as a secondary phenomenon usually when shock has persisted for several hours. Heparin and coumarin drugs, in doses that will not induce hemorrhage, do not interfere with the formation of these white thrombi.

Mechanisms of Death. In hospitals without coronary care units approximately 45% of deaths from acute myocardial infarction are caused by primary arrhythmias, 40% by pump failure, 10% from cardiac rupture (a form of pump failure), 3% from pulmonary or systemic arterial embolization, and 2% from noncardiovascular causes such as infection, hemorrhage, or renal failure.

Heparin and coumarin compounds have diminished greatly the morbidity and, to a lesser extent, the mortality from thromboembolic disease. The evidence is against the view

From the Departments of Medicine and Pathology, The Washington University School of Medicine and the Jewish Hospital of St. Louis, St. Louis, Missouri.

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that anticoagulants prevent or diminish coronary artery thrombosis, per se.

The question to be considered in this paper is whether new agents are available to prevent or diminish fresh coronary artery thrombosis, an aspect of coronary artery disease that has never before been attacked directly. The antiplatelet aggregant compounds have been proposed for the prevention of thrombi forming in the coronary arteries; thrombolytic drugs have been recommended as agents that might dissolve fresh thrombi so rapidly as to prevent or ameliorate the myocardial sequelae of coronary artery thrombosis. The preceding paragraphs have attempted to remind the physician of the complexities involved in evaluating drug efficacy in myocardial infarction, as well as to emphasize that trials with these new agents represent the first attempts to deal directly with the coronary artery thrombus itself. The subsequent portions of this report assess the current state of the art in these two approaches to the therapy of coronary artery thrombosis.

**Antiplatelet Aggregants**

**The Platelet Thrombus.** In the artery thrombosis can be readily visualized as an extension, or as an exaggeration, of the hemostatic plug that forms in response to injury such as may be seen on atheromatous plaques in coronary arteries. The various steps in this series of reactions have been the subject of a number of reviews.\(^4\)\(^-\)\(^9\) In brief, the adherence of platelets to subendothelial collagen or related material causes the release of platelet ADP and other factors, which in turn induce platelet aggregation. Collagen also is believed to activate Hageman factor (factor XII), thus initiating the sequential biochemical amplification system leading to fibrin gel formation. Thrombin, a by-product of the above reaction, is responsible for converting the loose and reversible ADP-induced platelet plug to a consolidated and irreversible phase with the entire aggregate contracting. The second effect of thrombin as it accumulates, of course, is on its principal substrate, fibrinogen, which is converted to fibrin, microscopic strands of which appear at the periphery of the platelet plug and further reinforce it. These overall series of reactions yield what is known classically as the hemostatic plug or the white or platelet thrombus—the predominant thrombotic lesion in the coronary arteries. It is becoming increasingly evident that the interplay of various factors during the formation of the hemostatic plug are complex and that our understanding of the entire process is still limited. New information is continually being added: thus, in vitro data have recently been obtained showing that activated factor X can induce platelet aggregation in the absence of thrombin.\(^10\) This is of importance because activated factor X is an enzyme which is an obligatory intermediate in all known mechanisms of mammalian blood coagulation.

**Platelets as Markers of Hypercoagulability.** In the laboratory there are a variety of methods to assess platelet function. These include the bleeding time, turnover studies of labeled platelets, adhesiveness of platelets to glass and other foreign surfaces, platelet factor III assays, release of serotonin and platelet factor IV, platelet adenylylase and cyclic-AMP levels, and platelet aggregation induced by various agents. In fact, once the role of platelet aggregation in initiating white-thrombus formation was fully appreciated, there was a clear desire to study this phenomenon. The manufacture of a simple aggregometer, which permits turbidimetric measurement of platelet concentration, wherein optical density varies with platelet aggregation, has markedly facilitated such studies, and many compounds have been recognized as inhibitors of platelet aggregation.\(^7\)

Which agents known to modify platelet behavior are likely to be antithrombotic in arteries? Which assay or assays of platelet function should be used to monitor such antithrombotic activity? The answers to these questions are not presently available. In vitro, platelets can adhere to each other and to foreign surfaces. Thrombocytes can also release or take up various substances, initiate clot retraction, and change their shape as well.
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as their surface charge. There are, moreover, many descriptions and several studies of alterations in platelet function among patients with thrombotic disease or with pathologic states known to carry an increased risk of thromboembolism. Yet, there is no general agreement as to any differences in platelet function or morphology between normal individuals and patients with thrombotic disease, nor has it been determined whether or not an observed platelet abnormality is causal, coincidental, or subsequent to a thrombotic episode. In brief, there are no prospective studies demonstrating that any platelet abnormality clearly predisposes to the development of thrombosis in man. These correlative failures may, however, relate to deficiencies in methodologies for demonstrating platelet abnormalities on the one hand and, on the other, failure to employ techniques more sophisticated than careful clinical observation to determine whether thrombosis has occurred.

Antiplatelet Aggregate Activity and Thrombosis. Most studies of the effect of drugs on platelets have depended on in vitro systems, particularly aggregation. Several in vivo models have also been used in which the effects of antiplatelet aggregate activity on experimental arterial thrombi have been determined, but sometimes with conflicting results.

Because some of the pharmacologic compounds interfering with platelet aggregation are well tolerated by human subjects, some investigators have moved quickly to clinical trials. A few drugs such as dextran, aspirin, dipyridamole, prostaglandin E, glyceryl guaiacote, and clofibrate have been examined in man.

The most extensive investigations have been with dextran. In several series the incidence of thrombosis has been decreased by the use of this agent. A significant hazard is expansion of the blood volume with the risk of congestive heart failure. Dipyridamole has been demonstrated to decrease thromboemboli in patients with cardiac prostheses and to decrease platelet turnover in such patients. In contrast, the drug has not proved successful in treating cerebrovascular disease. In a recent series of postoperative hip fractures, aspirin, dextran, and warfarin were of equal value in reducing venous thrombotic complications, but dipyridamole was not as effective as these agents. In a preliminary report of another study, neither high nor low doses of aspirin reduced the number of positive fibrinogen limb scans in a series of postoperative patients. These various populations treated with aspirin and dipyridamole may not be comparable. Of interest is the fact that the effect of aspirin and prostaglandin E on platelets persists after the drugs have disappeared from the plasma. Further investigation of these agents in both arterial and venous thrombosis is required.

The use of antiplatelet aggregants to prevent coronary artery thrombosis is relatively new. Among reported studies, none has provided convincing evidence of prophylactic value, but long-term studies are not available. However, there is some evidence that dextran may be harmful to patients with acute myocardial infarction. The evaluation of these drugs will require not only large-scale clinical trials with all their inherent hazards but, because one is seeking to prevent rather than to treat thrombosis, these large-scale trials will have to be maintained for several years. Even if clinical improvement is demonstrated, it may be difficult to determine that the benefit resulted from an effect on the platelet. Dipyridamole and related compounds, for example, have measurable vasodilating properties that, in part, parallel their antiplatelet aggregate activity.

These comments are not intended to suggest that antiplatelet aggregants have no place in the prophylaxis of myocardial infarction, but rather to emphasize the considerable obstacles that must be overcome in the design and execution of clinical trials involving these agents. On the positive side of the ledger, many of the proposed drugs are inexpensive, relatively safe, easy to administer, and simple to monitor. Even if their contribution proves to be small, the gain would be real enough considering the size of the coronary disease.
problem in this country. The final judgment, however, is years away.

Thrombolytic Therapy
Mechanism of Fibrinolysis. As with fibrin formation, fibrin dissolution (fibrinolysis) occurs through a series of enzymatic reactions. Plasminogen, the inactive precursor of plasmin, circulates freely in the blood and is in the thrombus as the coagulum is formed. The thrombus itself stimulates the release, from adjacent damaged endothelial cells, of tissue activator which converts plasminogen both in the plasma and within the thrombus into the active proteolytic enzyme plasmin. Plasmin not only digests fibrin into soluble fragments, but also changes fibrinogen and several other clotting factors, notably factors V and VIII, into inactive compounds. This resulting potential for serious systemic hemorrhage is counterbalanced, in large measure, by the fact that plasma contains a plasmin inhibitor, antiplasmin, which inactivates circulating plasmin, thus protecting clotting proteins in the general circulation from degradation. Antiplasmin activity, however, is decreased within the thrombus and therefore does not interfere with plasmin digestion of the fibrin in the thrombus.

The fibrinolytic system is almost invariably activated at the same time as the coagulation sequence, possibly through the action of activated Hageman factor on both processes. Since plasmin enzymatically degrades fibrinogen and factors V and VIII, bleeding may result from excessive plasmin activity in fibrinolytic states caused either by disease or by therapeutically induced states of fibrinolysis. The questions whether coagulation and fibrinolysis are occurring continuously at low levels in normal subjects and whether increased coagulation or decreased fibrinolytic activity is a primary cause of thrombotic disorders remain unresolved.31, 32

Of importance conceptually in the development of thrombolytic therapy is the thesis proposed by Alkjaersig et al.33 that plasminogen is bound to fibrin in the process of thrombus formation. It is believed that the activation of plasminogen is different within the fibrin gel as contrasted with that soluble in the plasma, and that different activators possess different activities in each phase. Conversely, antiplasmin is believed to be less effective against plasmin within the thrombus than it is within the circulation at large. This concept suggests that a desirable thrombolytic agent could be given at a dose that would activate thrombus-bound plasminogen yet not significantly alter plasma plasminogen or other blood-clotting proteins. This view is the basis for believing that a plasminogen activator would be a more desirable thrombolytic agent to use than plasmin itself. Although this concept, developed by Sherry and his associates, is not subscribed to by some investigators,34, 35 these latter groups represent, at present, a distinct minority and the thrombolytic agents currently recommended for use in man are those substances which activate endogenous human plasminogen to plasmin. Additionally, the high in vitro gel/sol activity ratio of urokinase has in part been responsible for the great interest in this agent.36

Thrombolytic Agents. In vitro, a large number of diverse substances have been demonstrated to activate plasminogen. These include Hageman factor, streptokinase, urokinase, tissue activators, thrombin, trypsin, and a variety of chemical substances. Many of these agents are not suitable for use in animals or in man.

Two classes of drugs have emerged which have been subjected to in vivo tests. The first group includes such agents as streptokinase and urokinase, which are activator agents with sufficiently minimal side effects that their intravenous injection can be accomplished in animals and man. The second group of drugs include agents such as the sulfonylureas and certain anabolic agents like ethylestrenol that increase the level of circulating plasminogen activator. Although these latter drugs do not induce as potent a thrombolytic state as do streptokinase and urokinase, they have the advantages of being oral compounds that are more suitable for prolonged therapy. Also in

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this latter group are agents such as phenformin and metformin whose effects in animals and in man have been examined chiefly by Fearnley and his co-workers. These agents are being studied for their prophylactic effect in peripheral arterial disease rather than as agents to dissolve fresh thrombotic occlusions. No well-controlled trials have yet been conducted to evaluate their clinical efficacy. While in man these drugs alter tests of fibrinolytic function, the clinical significance of these changes is not clear.

**Streptokinase and Urokinase in Man.** The use of streptokinase in the treatment of acute myocardial infarction was first reported in 1959 by Fletcher and co-workers. This drug, however, has received less extensive trial in the United States than elsewhere where it has been employed in the treatment of venous thrombosis, pulmonary embolism, acute and chronic peripheral arterial occlusion, and acute myocardial infarction. The initial interest in streptokinase in the United States was dampened by the high incidence of side effects resulting from the infusion of this thrombolytic agent. With recent significant advances in the purification of streptokinase, therapy with this enzyme is presently undergoing a renaissance in this country.

Another reason for the delay in rediscovering streptokinase has been the development of highly purified preparations of urokinase which, although substantially more expensive, are devoid of the pyrogenicity, antigenicity, and the “resistance” inherent in the use of streptokinase. Presently, urokinase is undergoing a rigorous, multicenter, controlled trial in pulmonary embolism and the initial evaluation of the drug clearly indicates its capacity to enhance thrombolysis, although, as might have been anticipated, there has been no decrease in mortality among urokinase-treated patients with pulmonary embolism compared with their matched controls.

Originally, it had been believed on the basis of animal work that the efficacy of fibrinolytic therapy in dissolving thrombi was profoundly age-dependent, it being claimed that thrombi older than 7–10 days would be markedly resistant to dissolution. Several recent studies have cast doubt on these conclusions and have suggested, in the case of peripheral arterial occlusion, for example, that thrombi of many weeks’ duration may be susceptible to substantial resolution. If these findings are confirmed, an important extension of the role of thrombolytic therapy will be possible.

In other countries, there have been several published trials in which the role of streptokinase in myocardial infarction has been evaluated. Most of these trials have claimed some decrease in mortality in the treated groups, but many questions remain to be answered beyond the primary one of the adequacy of the trials themselves. These questions concern the differences in drug dosage schedules and the variable patient-to-patient response in terms of induced fibrinolytic activity.

One of the largest of these trials was published by Schmutzler and co-workers in Germany and involved 558 patients. They reported a mortality of 14.1% in the treated group compared to a mortality of 21.7% in the control population. This study was not randomized. A subsequent trial by the same group of investigators using a randomized series, compared streptokinase and anticoagulant treatment with anticoagulant therapy alone. Their preliminary findings show a mortality for the streptokinase-treated group of 13.2% compared with a 23.1% mortality in the control population. The P value was slightly under 0.05. These workers also believed that, in their first series, there was a significantly faster improvement in electrocardiographic abnormalities in the treated compared with the control group and that the “early use of thrombolytic therapy may reduce the extent of cardiac muscle necrosis.”

Amery et al. reported on a randomized series of 167 patients in which streptokinase did not reduce mortality as compared with heparin. A number of these same investigators subsequently conducted a larger trial with 764 patients. In the latter trial, overall mortality
was significantly lower in the streptokinase-treated group than the heparin-treated group (18.5 vs 26.3%; 0.027 P > 0.01), although in contrast to the German study there was not a significant difference in the mortality with the first 24 hours. The streptokinase group had more complications, chiefly bleeding and temperature elevations. The conclusion was that streptokinase effected a definite reduction in mortality, but that recommendations for its use would require further study, particularly in well-controlled coronary care units.

It is clear from the literature that there is a real and urgent need for a single, large, multicentered, controlled clinical trial to resolve once and for all the question of whether mortality in acute myocardial infarction can be favorably influenced by thrombolytic therapy. Before a definitive trial can be instituted, further data on the optimum dose and duration of urokinase therapy need to be obtained. Some of this information may hopefully be derived from the ongoing National Institutes of Health trial of urokinase in pulmonary embolism.

The rigorous and unending demands of an acceptable clinical trial in acute myocardial infarction are now well appreciated. This is also true of the capacity to define the patient population to be studied, which has been greatly facilitated by the existence of coronary care units and improved sophistication in monitoring the various clinical and laboratory parameters of myocardial infarction. If the trial population is adequate in size, and carefully supervised over a long enough period of time, it will be possible to recognize whether or not there are benefits to the overall treated population or whether there may be, in fact, benefits restricted to one or more subdivisions of the trial population. Difficult as it may be to demonstrate a decrease in mortality, an even greater problem will be the gathering of data to support the suggestion of several investigators that the size of the myocardial infarct may be reduced by thrombolytic therapy. There is real doubt as to whether adequate hemodynamic or pathologic data can be derived from a clinical trial to answer this question.

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STANFORD WESSLER and LAURENCE A. SHERMAN

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