look at the elements of these clotting systems and at the platelets, and one can begin to dissect out the etiology of clotting in these vessels. In cases that are resistant, it may be that the initiating event is not the reaction of the blood coagulation factors per se but the response of the platelets, and that the heparins and warfarin derivatives do not inhibit this response.

It is important, too, to keep in mind the role of antithrombin III, a co-factor for heparin. Without it there cannot be a balanced clotting mechanism. The recently recognized heparin co-factor may be deficient in some people, leaving them with a predisposition to clotting. Such situations, if not identified, will lead to an inadequate response to heparin when it ordinarily would provide effective therapy.

One must also consider the difficulties with arterial diseases. We recognize arterial thrombosis as either a blood clot in an artery that seems to have a normal surface, or a blood clot in a vessel in which the surface has been significantly altered by atherosclerosis.

In the past there have been fads in the treatment and prevention of thrombotic diseases with the warfarin derivatives, which have been in and out of favor for use in long-term prevention. Recent information suggests that some people who have changes in vessels may very well not have adequate coagulation mechanisms, and that their clots are not alone due to the conversion of fibrinogen to fibrin. Their thrombi may in some way be related to the alteration of fats, lipids, triglycerides, and other substances that may help initiate or perpetuate vessel-wall abnormalities.

Platelets Alter Vessel Wall

There seems to be a very intimate relationship between the platelets sticking to the blood vessel wall and an alteration in the vessel wall, all of which may perpetuate the system. There is even some very suggestive laboratory evidence that the platelets being sequestered near the surface walls of other platelets may actually promote changes in the vessel wall, and that this in turn makes it easier for the platelets to adhere to it.

And remember, not all arteries are closed by clots. Some are blocked by pure atherosclerotic plaque. Evidence has been found that alteration of blood vessel walls in classical atherogenesis can be produced by platelets releasing substances that act on the walls. Consequently, in the search for ways to prevent arterial vascular disease, one now may begin to investigate agents that eliminate or interfere with the platelet attaching itself to the vessel wall.

We are beginning to get a handle on mechanisms that produce coagulation problems, by studying the causes. Is it the coagulation mechanism, together with various other interactions, that set off the cascade of clotting factors that actively leads to the final deposition of fibrinogen as the main cause of the clot? Or is it the platelet-vessel wall interaction that initiates the formation of what we call "platelet plug," which is as effective a clot as the fibrinogen plug in stopping blood flow? If one can answer these questions, one can give more rational therapy, and that is the key to this whole question.

Key to Thrombus Prevention

The heparin-like drugs are basically compounds that attack the final depositions and the conversion of fibrinogen to fibrin. If the clot was not formed by this pathway, those drugs will not work. On the other hand, if the platelet-vessel wall interaction is the initiating factor, we now have drugs that in vitro or in vivo can alter platelet responsiveness, and may be the key to the prevention of arterial and/or venous thrombus formation.

Warfarin derivatives have been used for major prevention of venous and arterial clots because of their ease of administration and relatively low rate of complications. They slow the coagulation cascade to retard the formation of fibrin. They do not, however, affect platelet function, and cannot prevent fibrinogen conversion.

In addition, in an age of multiple drug use, we are recognizing more and more drug-drug interactions that affect warfarin derivative metabolism, making the simple monitoring of these drugs by the familar prothrombin-time more difficult. An ideal, easy-to-administer, appropriate inhibitor of fibrinogen conversion is not available. However, more reports are appearing, suggesting that self-administered, low-dose, subcutaneous heparin may be an effective measure for the prevention of venous thromboembolic disease.

There are arterial diseases and there are venous diseases. Major ones are caused by the coagulation mechanism; some are possibly caused by platelets. The arterial diseases look more and more as though they are influenced by the platelets. It is possible, in a highly sophisticated medical center, to do complex laboratory tests that might give an indication, but as yet we do not have appropriate methods widely available for the primary care physician. Investigations are continuing, however, and one hopes they will lead to rational use of the heparin drugs and the anti-platelet drugs. □

NEXT IN THE SERIES: Heparin—when and how it should be used, and when it should probably not be employed, based on what is proved, what appears probable, and what is indicated by recent research.