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Role of Platelets in Hemostasis and Thrombosis

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Platelets interact with the coagulation factors in a complex way to arrest bleeding or generate thrombi. Recently, the platelet's relationship to endothelial alteration and atheroma production has received renewed attention. At present, tests of platelet function better define "hypocoagulable" rather than "hypercoagulable" states.

Hemostasis

UNDER NORMAL CONDITIONS (Figure 1), whenever a blood vessel is severed, several responses occur to staunch the flow of blood. If the vessel has a muscular coat, vascoconstriction occurs. In all vessels, the interface between vessel and blood is altered, promoting platelet adhesion to newly exposed subintimal structures. These adherent platelets release adenosine diphosphate (ADP) and cause other platelets to release more ADP, to form aggregates and ultimately to form a platelet plug. Platelet membrane phospholipid becomes available along with trace amounts of thrombin generated via the extrinsic pathway. The phospholipid and thrombin intensify the production of more thrombin[1,2] which began when the subintimal structures activated the contact factors—factors XII and XI. Thrombin is independently a strong inducer of platelet aggregation and simultaneously leads to fibrin formation with enlargement and impermeability of the platelet plug (Figure 2). Reduced blood flow and more thrombin production promote more fibrin deposition within minutes of the event. In time, white cells invade the thrombus.[3] Later, thrombus dissolution occurs as plasminogen, initially absorbed from the plasma and trapped within the thrombus, is altered to plasmin.[4] Completion of the healing process, when it occurs, involves recanalization and reconstitution of the endothelium. The recreated vessel may be normal, or there may be persistent abnormalities in the vessel wall with alterations in blood flow.

Therefore, hemostasis is the process that maintains the blood within the blood vessels. It is a complicated but efficient mechanism interlocking responses of the blood vessels, the platelets, the coagulation factors and the fibrinolytic mechanism.

Platelets: History

Platelets, a tenth the size of red cells, were discovered in the middle of the 19th century when a microscope with sufficient power became avail-

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ABBREVIATIONS USED IN TEXT
ADP = adenosine diphosphate
AMP = adenosine monophosphate
ASA = acetylsalicylic acid
ATP = adenosine triphosphate
LASS = labile aggregation stimulating substance
MDA = malonyldialdehyde
PG = prostaglandin

able. A major conflict developed: Were the platelets artifacts, white cell granules, or the precursors to either the white cell or the red cell? Almost no one associated platelets with fibrin formation.

In 1882 the experiments of Bizzozero of Turin[5] showed that the initial stages of thrombosis involved platelets. Still, by the turn of the century many investigators felt platelets were either artifacts or at best of minimal importance. Platelets were still cells in search of a function.

In 1905 Pratt[6] developed the first method to count platelets and in 1910 Duke[7] added the "bleeding time." Eventually, modifications of this method would be used to differentiate between qualitative and quantitative defects in platelets. The next major advance occurred when electron microscopy was used to examine platelet morphology.

INTERLOCKING PATHWAYS OF PLATELET AND COAGULATION FACTOR ACTIVATION I

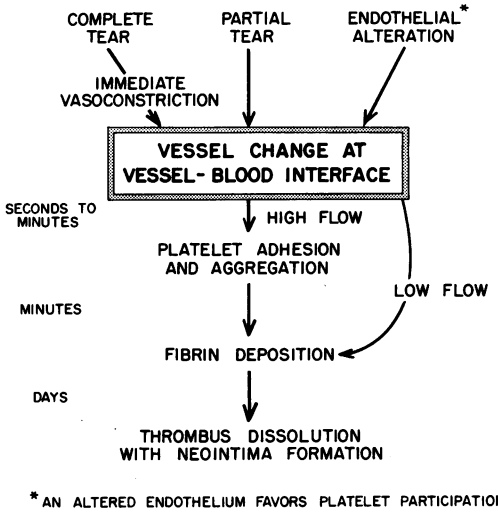

Figure 1.—Shown is a schematic representation of the normal response of blood to changes in the vessel wall. The effects of disordered flow as well as the interactions of the platelets and coagulation factors have been omitted (see Figure 2). These reactions may be inappropriately triggered by endothelial cell changes or abnormal flow leading to thrombosis rather than hemostasis. These stimuli that lead to thrombosis probably favor greater platelet participation in the process.

In 1960 Gaarder and co-workers[8] showed that adenosine diphosphate aggregates platelets suspended in plasma. With the development of platelet aggregometry by Born in 1962,[9] an explosion in platelet research occurred to form our present-day understanding of the platelet functions in hemostasis and thrombosis.

Platelets: Their First Function

Platelets respond to a variety of substances by altering their shape, adhering to the material to which they are exposed, changing their ectomembrane constituents and undergoing the "release reaction." Substances shown to produce this reaction include materials as diverse as proteolytic and structural proteins (such as thrombin and collagen), vasoactive materials (such as serotonin and epinephrine), nucleotides (such as ADP), polypeptide hormones (such as vasopressin) and nonbiologic surfaces (such as glass, latex particles

INTERLOCKING PATHWAYS OF PLATELET AND COAGULATION FACTOR ACTIVATION II

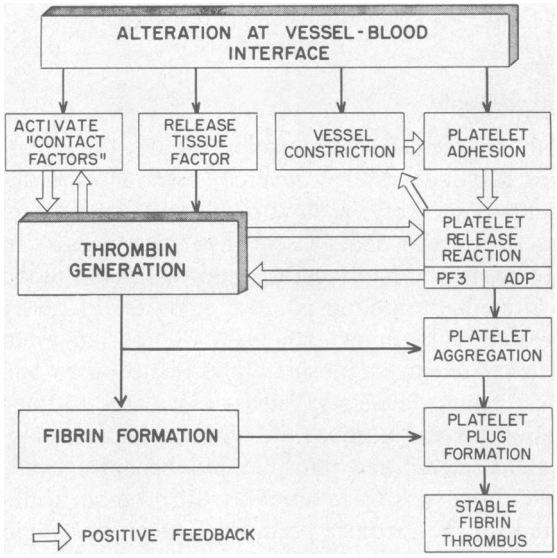

Figure 2.—The production of thrombin in response to vessel wall changes is begun by activation of the coagulation factors and release of tissue factor, and amplified by the presence of the platelet surface and autocatalytic mechanisms. Similarly, platelet recruitment to form a plug has a "positive feedback" quality because the release of stored adenosine diphosphate (ADP) promotes further release of ADP. Therefore, prevention of these reactions is most effective when the vessel wall alteration is prevented. Once these interlocking reactions are initiated, the process can only be blunted. Acetylsalicylic acid acts to prevent the release of ADP from the platelet; it does not affect thrombin generation or the other platelet reactions. PF3 indicates platelet factor 3.

and polyvinyl chloride).[10] The release reaction involves an explosive movement of intracellular granules to the center of the platelet. Degranulation releases cations, vasoactive amines, proteins, nucleotides and other materials into the plasma via an intricate canulicular system.

The release reaction has been divided into two types according to the agonist that produces the reaction. Type I agonists—ADP, epinephrine and collagen—release a number of constituents; for example, nonmetabolic adenosine triphosphate (ATP) and ADP, serotonin, calcium and platelet factor 4 (PF4). The stronger type II agonists (of which thrombin is the only physiologic agent) release additional constituents: for example, fibrinogen and lysosomal enzymes.[10]

Evidence is accumulating that underlying the response to these various stimuli there is a basic mechanism involving all three second messenger systems: the obligate intermediates of prostaglandin (PG) synthesis, calcium ions, and cyclic adenosine monophosphate (AMP).[11] A reasonable hypothesis (Figure 3) presently being tested in several laboratories is that platelet agonists interact with specific receptor sites on the membrane, activating phospholipase A_2.[12] Arachidonic acid,

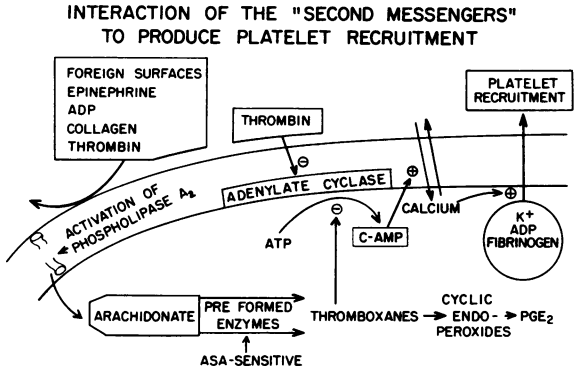

Figure 3.—Platelets are responsive to a number of different stimuli, and in turn respond in a relatively uniform fashion by serially (1) activating membrane phospholipase, (2) releasing arachadonate into the cytoplasm, (3) producing prostaglandins (PG), (4) depressing adenylate cyclase activity, (5) diminishing a pool(s) of cyclic adenosine monophosphate (C-AMP), (6) promoting greater entrance of calcium into the cell and (7) releasing preformed packets and other cytoplasmic constituents into the extracellular space. The materials released include adenosine diphosphate (ADP) which promotes platelet recruitment into the platelet plug. Acetylsalicylic acid (ASA) prevents the formation of the intermediates of PG (labeled "thromboxanes") and therefore diminishes the extent of the "release reaction" by this mechanism. Thrombin may act at multiple sites including a site distant to the ASA-induced change to allow platelets to participate in hemostasis. ATP indicates adenosine diphosphate.

which exists in large quantities in the platelet and specifically as part of the membrane phospholipids,[13] is released into the cytoplasm by this enzyme. There this fatty acid is transformed by one of two parallel preexistent enzyme systems into the prostaglandins E_2 and $F_{2\text{-alpha}}$ (PGE_2 and $PGF_{2\text{-alpha}}$) with the formation of very important intermediates. These intermediates—an endoperoxide (labile aggregation stimulating substance, LASS), cyclic ethers (thromboxames) and other PG's—may have ancillary functions; for example, vasoconstriction.[14-17] Presumably one of these intermediates is the common denominator producing the same or a similar "release reaction" in response to all or many of the various platelet agonists. The prostaglandins E_2 and $F_{2\text{-alpha}}$ are produced in relatively small amounts by these transformation pathways and functionally are not nearly as important as some of the more prevalent intermediates.

Collagen, thrombin and epinephrine have been shown to depress membrane adenylate cyclase activity and, therefore, platelet cyclic AMP pools, but the relationship of this biochemical event to platelet aggregation is unclear.[18] These two second messengers interact since increases in PGE_2 and $PGF_{2\text{-alpha}}$ production depress adenylate cyclase activity.[19] Calcium—another second messenger in many cells—is also important for platelet reactivity. Translocation of calcium between intracellular pools is crucial to the "release reaction."[20,21] How the three "second messengers"—PG's, cyclic nucleotides and divalent cations—interact to presumably produce adhesion, release, aggregation and the eventual promotion of a gelatinous thrombus by fibrin production is still not completely clear. Partial blockade of this subcellular mechanism still may not prevent platelet participation in hemostasis. The effect of acetylsalicylic acid (ASA) on platelets is an example of partial blockade. ASA and severe thrombocytopenia do not produce equivalent degrees of bleeding or prolongation of the template bleeding time. Platelets exposed to ASA can participate in plug formation[22] and therefore in hemostasis.

The mechanism by which a thrombus stops propagating is not immediately obvious. Thrombin is autocatalytic to its own production,[23] and is produced in increasing amounts in the microenvironment of adherent, activated platelets.[24,25] Similarly, activation of platelets is promoted by thrombin and leads to more platelet activation. Both these interlocking events—thrombin produc-

tion and platelet activation—are therefore positive feedback systems in contrast to the "negative feedback" mechanisms characteristic of hormonal regulation. Extension of the thrombus is regulated by flow—producing dilution of platelet aggregates and activated factors. In addition, thrombin produces competitive inhibitors of the coagulation cascade by proteolytic digestion of previously activated coagulation proteins.[25-27] These fragments also limit the size of the thrombus. The physiologic role of the antithrombins in modifying thrombus growth is unknown.

Hemostasis Versus Thrombosis

Thrombosis is not equivalent to hemostasis, but is a distortion of the hemostatic process. Both hemostasis and thrombosis involve the vessel wall, the fibrinolytic system, the coagulation factors and the platelets to produce an endovascular insoluble matrix of fibrin, erythrocytes and leukocytes. Both have common modifiers; for instance, the rate of blood flow. The relative participation of platelets and the soluble coagulation factors in the early interactions with the vessel wall is probably very dependent on the velocity and quality of blood flow. Rapid or disordered flow promotes vessel wall-platelet and platelet-platelet interaction; slow flow may lead to a thrombus composed primarily of fibrin. Some of the differences between thrombosis and hemostasis are now evident. The trigger to hemostasis is a change in the vessel wall and the primary platelet agonist may be extravascular collagen. However, thrombosis can occur because of a change in flow, a vessel wall abnormality or "hypercoagulability" of the blood. Platelets may react to another abnormality (the suspicion is that it may be intravascular thrombin or that they may themselves be the trigger to inappropriate thrombus formation). In the future, platelet-suppressive drugs may be able to control the thrombotic response without impairing hemostasis. In fact, there is circumstantial evidence to suggest that aspirin and other drugs may accomplish this task. Clinical trials are underway but, as yet, there is no definite evidence that platelet-active drugs are antithrombotic.

Partial blockade of platelet function may be an important phenomenon in clinical medicine. There is no doubt that ASA (as the best known example among numerous drugs) blunts the platelet's capacity to participate in hemostasis. It is not complete blockade; platelets affected by ASA still produce a platelet plug faster than diminished numbers of platelets or no platelets at all. There must be an alternative ASA-insensitive mechanism for the production of platelet aggregates. Thrombin-induced aggregation and release may be this mechanism. The best data to support this suggestion are the experiments of nature in man in which thrombin and fibrin formation are seriously impaired. When factor VIII and factor IX deficient subjects have been treated with ASA,[28] the bleeding time has been, in most instances, notably prolonged. In some of these persons, administration of the deficient soluble coagulation factor was necessary to stop bleeding at the bleeding time site. Fibrin deposition alone cannot be used to explain the prolongation of the bleeding time after ASA administration because this mechanism may be completely intact in people with afibrinoginemia.[29] Therefore, platelets must participate in the cessation of bleeding of a person who has ingested ASA. These findings, taken together, strongly suggest that thrombin or some other intermediate in the coagulation cascade can produce effective platelet function when acetylsalicylic acid has blunted platelet aggregation and release.

It is not clear at the present time what the physiologic mediators of *in vivo* platelet function are. Traditionally, ADP and collagen are considered to be important. However, the intravenous infusion of ADP does not lead to a retractable impermeable plug. ADP produces only reversible aggregates *in vivo*.[30] There is evidence from some reports to suggest that thrombin may be a major, if not the dominant, mediator of platelet adhesion, aggregation and release *in vivo*[31,32] although other reports disagree.[33] Thrombin may be capable of causing release of serotonin from platelets despite ASA's prevention of PG production as shown by Smith and Willis (Figure 3).[34] It has been known for some time that thrombin produces a more profound change in the platelets than most other platelet agonists.[35] There is some evidence to suggest that there are multiple receptor sites on platelet membranes for thrombin,[36] again suggesting alternative mechanisms of platelet activation, some of which may be ASA-sensitive and others of which may be ASA-insensitive. Thrombin's role may explain why ASA blunts but does not cripple hemostasis.

Platelets: Their Other Functions

This analysis of platelet function has emphasized its role to promote hemostasis and to partici-

pate in thrombogenesis. Other functions for platelets are also known:

- Platelets cause leukocytes to accumulate around the platelet plug; that is, they may release chemotactic substances.[37,38]
- Platelets do release vasoactive amines.[39]
- Platelets may release hydrolytic and proteolytic enzymes directly into the intimal and subintimal structures provoking changes that may eventually lead to atheroma.[40]
- Platelets act to transport serotonin from sites of synthesis (the gut) to other sites of function.

At least some of these functions relate to the two-edged sword of hemostasis-thrombosis.[41]

Tests of These Functions

Laboratory tests of platelet function have traditionally been designed to test platelet "hypofunction"; that is, inability to respond fully to a hemostatic challenge. These tests include the bleeding time,[42] platelet count, morphology, clot retraction, prothrombin consumption, adhesion, aggregation in response to a number of agonists and release of serotonin or platelet factor 3 (PF3). In addition, acid phosphatase can be used *in vitro* and platelet survival (using ^{51}Chromium[43] or malonyldialdehyde [MDA][44]) *in vivo* to assess platelet kinetics.

Recently, investigators have attempted once more to overcome their frustrations and test the role of platelets in mediating thrombotic diseases such as stroke, myocardial infarction and atherosclerosis. *In vivo* platelet survival is being reevaluated and other tests have been added. Some of these newer, less invasive, procedures attempt to evaluate platelet turnover by measuring platelet specific proteins that normally are not detected in cell free plasma. These tests include the platelet factor 4 analysis,[45] release of specific isoenzymes[49] and beta-thromboglobulin assay.[48] Platelet turnover may also be indirectly measured by platelet sizing[47] because platelets newly released from the marrow are bigger than the general population of platelets. Increased numbers of circulating aggregates[46] may also be markers for platelet-mediated thrombotic events.

Further Reading on Platelets

For detailed reviews about platelet physiology, pathophysiology and use of platelet-suppressive drugs, the reader is referred to the articles by Weiss,[50] by Genton and co-workers,[51] by Mustard and Packham[52] and by us.[53]

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Initial Care in the Immediate Postburn Period

The magnitude of the injury in a burn patient depends both on the depth of the burn and its extent. And as far as burn wound depth goes for hospital care, the important differentiation is between partial (or second degree) burn and third degree burn, in which all skin appendages have been destroyed and some grafting is required for definitive coverage. This is important in terms of function and of need for grafting. More important in the initial care is the extent of burn which can be most readily assessed, using the rule of 9's where various anatomical divisions of the body represent 9 percent or a multiple thereof (the upper limb is 9, lower limb is 18, anterior or posterior trunk 18 each, head and neck 9, perineum and genitalia 1).

In the initial care of a burn patient, one directs his attention to establishment of a secure intravenous pathway for the administration of resuscitation fluids; determination of the need for a tracheostomy (and that is seldom today); the need for an escharotomy . . . ; tetanus immunization (a booster if the patient has had prior active immunization; otherwise, begin active immunization and give hyperimmune tetanus antiserum). Now, in the only instance where wound care takes any precedence at all is in the case of patients with chemical injuries where the severity of the burn depends not only upon the concentration of the agent to which there has been exposure but also upon the duration of contact. And in patients with chemical burns, immediate dilution of the offending agent with copious water lavage should be carried out.

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