PLATELETS AND ISCHEMIC HEART DISEASE

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Introduction

In the last 25 years, much attention has been paid to possible relationships between atherosclerosis and blood platelets. This interest has intensified in the last decade, particularly with the undertaking of 8 large multi-center secondary prevention clinical trials that tested the effect of various platelet-active drug regimens on complications of atherosclerotic heart disease. Four of these trials have reported their results within the last year. At least 12 more trials with platelet-active drugs that are examining cardiac complications as a primary or secondary endpoint are currently underway or in advanced planning stages.

This morning, I shall review much of the data regarding the relationship of platelet function and ischemic heart disease. I shall touch briefly on the role of platelets in the development and progression of atherosclerosis. I shall address three questions: 1) Do patients with atherosclerotic heart disease have enhanced platelet reactivity? 2) Can platelet-active drugs decrease the incidence of complications of some of these patients? 3) What is the proper role for platelet-active drug therapy for these patients today, given our current state of knowledge?

Platelet functions.

Platelet adhesion and aggregation reactions that occur normally during the clotting mechanism following trauma to vessels are similar to platelet adhesion and aggregation at sites of damage to the endothelium of vessels.(M1,W1) Adhesion to subendothelial collagen and exposed basement membrane is associated with a series of morphological changes of platelets. They change from an ellipsoidal to round shape, develop pseudopods and degranulate. Following adhesion to collagen, the platelets rapidly (within 1-2 minutes) release adenosine diphosphate (ADP) from their dense granules and also generate biologically active arachidonic acid derivatives, prostaglandin endoperoxides and thromboxane A_2, which diffuse into the plasma.(B1,S1,Z1) The highly active prostaglandin derivative, thromboxane A_2(H1) is generated by the following reaction sequence:

Membrane Phospholipids

↓ Phospholipase A_2

Arachidonic Acid —(Fatty Acid Cyclooxygenase)→ PGG_2 and PGH_2 (Cyclic Endoperoxides)

↓ Thromboxane Synthetase

Thromboxane A_2

These products of the release reaction cause additional circulating platelets to cohere to the initial ones which rapidly converts the adhering platelets into a multicellular platelet plug.(M1) The release reaction (M2) also liberates other materials, from the α granules, which is slower, occurring for as long as several hours. The dense granules contain vasoactive substances, such as serotonin. The nondense α granules contain a variety of proteins including platelet factor 4, β-thromboglobulin, and platelet mitogenic factor (a substance that promotes smooth muscle cell and fibroblast growth and migration). Other substances that are released include enzymes, coagulation proteins, and fibrinogen.(M3) Fibrin formation stablizes platelet plugs.(N1) If fibrin does not form around the aggregated platelets, the platelets that are not directly adherent to the vascular wall disaggregate and return to the circulation.

Platelets probably do not adhere to intact endothelium of veins or arteries under normal circumstances.(S2) This may result from endothelial cell production and release of prostaglandin I_2 (PGI_2, prostacyclin), a powerful inhibitor of platelet function.(M4) PGI_2 is generated in the endothelial cells by the following sequence of reactions:

Membrane Phospholipids

↓ Phospholipase A_2

Arachidonic Acid

↓ Fatty Acid Cyclo-oxygenase → PGG_2 and PGH_2 (Cyclic Endoperoxides)

↓ 6,9 oxycyclase

PGI_2

PGI_2 increases platelet cyclic AMP (cAMP) levels by stimulation of platelet adenyl cyclase.(M5) The raised cAMP level interferes with platelet aggregation, (M4) the release reaction, and perhaps with platelet adhesion to endothelium. Also, PGI_2 is a potent dilator of the coronary system and its production may be a major response of coronary arterial endothelium to mechanical, neural, hormonal, or hypoxic stimulation.(A1) PGI_2 production is reduced in vessels with arterosclerotic plaques compared to normal vessels in the same individual.(N2)

In order for blood platelets to contact subendothelial collagen, integrity of the endotheliolium must be interrupted. This may occur at atherosclerotic plaques. Other stimuli can also initiate the aggregation process *in vivo* including circulating catecholamines, ADP, some prostaglandins, immune complexes, fatty acids, and excessively turbulent blood flow.

Collagen-induced platelet ADP release and aggregation require the presence of Ca^{+2}. The requirements for these reactions have been investigated more extensively than the requirements for Ca^{+2} for platelet adherence to collagen, (S2) but there is some evidence that platelet adherence to collagen is optimal in the presence of divalent cations. (C1,C2)

Other factors influence platelet function. These factors include sex, smoking habits, diet, and hypercholesterolemia.(H2) There is some evidence that smoking- and cholesterol-induced platelet abnormalities may be mediated by increased thromboxane A_2 production. Diets high in flesh that are rich in eicosapentaenoic acid and poor in arachadonic acid (e.g. many fish) favors platelet production of thromboxane A_3 over the more potent proaggregatory thromboxane A_2. This may explain, in part, the low incidence of ischemic heart disease in Eskimos, whose diet is rich in eicosapentaenoic acid. (D1) Other, less well understood, factors may also be important. For example, a phospholipid leucocyte product that is a potent platelet activating factor has recently been discovered and characterized. (C3)

Platelets and atherogenesis.

Over a century ago, Von Rokitansky propounded the encrustation theory of the cause of atherosclerosis - the idea that surface deposits on arteries are incorporated into the intima giving rise to thickening and eventually atherosclerosis.(R8) The report in 1974 of a platelet mitogen that stimulates growth of smooth muscle cells and fibroblasts raised the possibility that platelet deposition on arteries and release of the platelet mitogen may be an important part of the atherogenic process. (R9) This hypothesis has been elegantly tested in three animal models of atherosclerosis, rabbits subjected to arterial injury with a balloon catheter and an atherogenic diet, baboons with induced homocystinemia, and pigs fed an atherogenic diet. Interference with normal platelet function by induction of thrombocytopenia (rabbits), drugs (baboons) or the pig model of Von Wilebrands disease interfered with development of atherosclerosis in these animal models. (F5,F6,H18)

It is, of course, speculative to extrapolate the data from the atherosclerotic animal models to atherosclerosis in man. The data showing enhanced platelet activity in young people with strong risk factors present for arteriosclerosis are the strongest data now available to support a role for platelets in human atherogenesis.(F7) A long-term primary prevention trial with platelet active drugs to test the hypothesis that interference with platelet function will diminish or prevent atherosclerosis in men is being contemplated, but results are obviously many years away.

Platelet Reactivity and the Complications of Atherosclerotic Heart Disease

Ischemic heart disease almost always occurs in the presence of atherosclerosis of a major epicardial coronary artery of a degree

that is at least sufficient to decrease blood flow through the artery during exercise. To be hemodynamically significant, the cross-sectional area of the artery must be reduced to less than 1/4 of the normal area. (B13) Exertional angina pectoris usually occurs when myocardial oxygen demand of the muscle subserved by the affected coronary artery exceeds oxygen delivery. (R6) The ultimate causes of other complications of ischemic heart disease are less clear. While transmural myocardial infarction often results from acute coronary artery thrombosis, many episodes of infarction occur in the absence of pre-infarction coronary thrombosis. (R7,B14,B15,H15,B16) The cause of deterioration of angina from a stable to an unstable syndrome is also unclear, but often appears to result, at least in great part, from transient, reversible limitations in coronary blood flow. (S22,F4,G4,M18,M19,N6,N7,M20) Sudden cardiac death is thought to result from ventricular fibrillation, or less commonly from high-grade heart block or asystole, but the factors responsible for the electrical events are also unclear in most patients. (P4). Coronary arterial spasm is regarded as the cause of variant (Prinzmetal's) angina. (H14) It has also been suggested that coronary artery spasm may be involved in causing some episodes of myocardial infarction, (M18) exertional angina pectoris, (Y2) and spontaneous angina pectoris at rest without ST-segment elevation. (M19) The cause of the spasm, however, is uncertain. (H14)

There are several ways that enhanced platelet reactivity could contribute to all of these complications. Abnormal platelet reactivity could increase platelet aggregation and formation of a platelet plug near an atherosclerotic plaque. These plugs could lead to coronary thrombosis or break up. In the process of dissolution of a transient platelet plug, platelet microembolization of the smaller coronary vessels would be likely. Some evidence suggests that platelet microembolization may be a factor in sudden cardiac death. (J1,H12,H13,E7) Thromboxane A_2 formation could cause or enhance coronary spasm.

Several types of animal investigation have lended credence to the postulate that enhanced platelet aggregation *in vivo* could participate in complications of ischemic heart disease in men. Intravascular platelet aggregation and subsequent myocardial damage has been produced by infusions of ADP and epihephrine in experimental animals (J2,H16) and was prevented by the previous administration of antiplatelet drugs. (H17) Cyclic changes in coronary blood flow in dogs with experimental stenosis were attributed to transient platelet plugs, which could be prevented by antiplatelet drug administration.

In vitro and *ex vivo* analyses of platelet function of patients with ischemic heart disease have yielded somewhat disparate results. The various types of studies and the results in patients with ischemic heart disease are reviewed below.

Assessment of Platelet Reactivity *In Vitro* and *Ex Vivo*

Platelet adhesion

Platelet "stickiness" has been studied by several techniques that are based on the propencity of platelets to stick to glass. (S3) Most

investigators have added their own modifications, but they all test platelet adhesion to glass test tubes, glass beads, or glass wool. Virtually all studies of platelet adhesion of patients with atherosclerotic heart disease used glass-adhesion studies. Recently techniques that use collagen-coated glass rods and everted, de-endotheliazed rabbit aorta strips have been devised,(C1) but have not been used to any substantial degree to test platelet function of patients with atherosclerotic heart disease. Platelet adhesion studies with patients with atherosclerotic heart disease can now be thought of as chiefly of historical interest. These procedures are subject to much variation and appear to be influenced by a number of factors that are hard to control such as diet, time of day, and season of the year. Nevertheless, many of these studies, most carried out in the 1950's and 1960's suggested that platelets of patients with ischemic heart disease were abnormally sticky. The results of most of those studies are outlined in Table 1. The studies are listed according to the year in which they were published. Note that all the studies from 1949 to 1967 were positive and all the studies since then were negative.

Platelet aggregation *in vitro*

Platelet responsiveness may be tested *in vitro* by measuring spontaneous aggregation or by determining the responsiveness to various aggregating agents. ADP, epinephrine, collagen, thrombin, or arachidonic acid may be used. The method most commonly used is that of Born.(B2) Light transmission through continuously stirred platelet-rich plasma is recorded. With increasing aggregation, there is an increasing percentage of light transmission (%T). An initial small decrease in %T, owing to change in platelet shape from discs to spheres, precedes the platelet aggregation-induced increase in light transmission. ADP, epinephrine and collagen are the most frequently used aggregating agents. The light transmission patterns of aggregation vary with the stimulus used and its dose. Low doses of ADP yield a rapid but slight increase in the %T followed by gradual disaggregation. With higher doses of ADP, a second wave of aggregation is noted reflecting intraplatelet ADP release and thromboxane A_2 generation. At even higher doses, the first and second waves of aggregation merge into a rapid monophasic pattern. When platelets are incubated with collagen, there is a lag period during which platelets adhere to collagen, followed by a monophasic aggregation wave owing to ADP release and thromboxane A_2 generation. When platelets are incubated with epinephrine, there is a rapid first wave of aggregation without induction of any alterations in platelet shape. A second wave follows reflecting ADP release and thromboxane A_2 generation. Even with large doses, the pattern is never monophasic. Platelet reactivity has been assessed by various techniques including: maximum change in %T, time to maximum aggregation, initial rate of aggregation, half-time of aggregation, minimum stimulatory concentration of aggregating agent necessary to achieve a given level of

TABLE 1.

ABNORMAL PLATELET ADHESION IN PATIENTS WITH ATHEROSCLEROTIC HEART DISEASE

Study	Year	Ref #	Results
Moolten, *et al*	1949	M14	+
Eisen	1951	E1	0
McDonald & Edgill	1959	M15	+
Horlick	1961	H7	+
Nestel	1961	N4	+
Murphy & Mustard	1962	M10	+
Moolten, *et al*	1963	M16	+
Pfleider & Rucker	1964	P3	+
Baumgarten, *et al*	1967	B10	+
Besterman, *et al*	1967	B11	+
Stormorken	1970	S17	0
Besterman, *et al*	1971	B12	0
Sjogren, *et al*	1971	S18	0
Steele, *et al*	1973	S12	0

TABLE 2.

ABNORMAL *IN VITRO* PLATELET AGGREGATION OF PERIPHERAL BLOOD IN PATIENTS WITH ATHEROSCLEROTIC HEART DISEASE

Study	Year	Ref #	ADP	Epi.	Throm.	Col.	Spon.	Dis.
Murphy & Mustard	1962	M10					0	
McArdie, *et al*	1966	M11					+	
O'Brien, *et al*	1966	02	+	0				
Zahavi & Dreyfuss	1969	Z2	+					+
Yamazaki, *et al*	1970	Y1	+					
Renaud, *et al*	1970	R5	0		+			
Goldenfarb, *et al*	1971	G2	+					
Sano, *et al*	1971	S15	+					
Salky & Dugdale	1973	S11	0			+		
Steele, *et al*	1973	S12	0			0		
Davis	1973	D6						+
Dreyfuss & Zahavi	1973	D5	+					
Frishman, *et al*	1974	F1	+					
Frishman, *et al*	1976	F2	+	+				

ADP = adenosine diphosphate; epi. = epinephrine; throm. = thrombin; col. = collagen; spon. = spontaneous; dis. = dissaggregation.

aggregation (S3) and the time required for disaggregation. (D6)

The same problems that plague the performance of platelet adhesiveness studies plague *in vitro* aggregation studies and I think that they, too, can be thought of now chiefly for their historical interest. The results of most of the studies of platelet aggregation in patients with ischemic heart disease are outlined in Table 2. While the results are conflicting, about half of the studies noted a hyperaggregable state of the platelets of patients with ischemic heart disease compared to control patients. Unlike the studies of platelet adhesion, recent as well as previous studies have reported positive findings.

The *in vitro* aggregation of platelets from simultaneously drawn coronary sinus and aortic samples was compared by Mehta *et al.*(M12) They found that the platelet count was lower in blood from the coronary sinus than from the aorta. They reported that *in vitro* ADP-induced platelet aggregation was lower in platelets from coronary sinus than from the aorta. They interpreted these data as being consistent with removal of hyperaggregable platelets in the diseased coronary vessels. Platelet aggregability was changed only for the coronary sinus platelets during pacemaker-tachycardia-induced ischemia and they suggested that the tachycardia-induced ischemia might be related to enhanced platelet aggregation of the atherosclerotic coronary vessels.

Platelet electrophoretic mobility.

Hampton and his associates described a technique of assessing platelet function based on the electrophoretic mobility of platelets exposed to ADP or epinephrine and found abnormal mobility of platelets with ischemic heart disease. (H8,H9) This method has not been used widely.

Circulating platelet aggregates.

Several methods have been devised to quantitate the presence of platelet aggregates in the circulating blood.(S3) The most commonly used technique is based on the finding that circulating platelet aggregates can be stabilized in a buffer containing low concentrations of formaldehyde. The ratio of the platelet count in platelet rich plasma from blood with formalin to blood without formalin gives a platelet aggregate ratio and presumably reflects the number of circulating platelet aggregates.(W2) While this technique has the appeal of presumably more nearly measuring an *in vivo*, instead of an *in vitro*, phenomenon, many investigators have not been able to duplicate the original results of Wu and Hoak. The technique has been extended recently to the study of the platelets of patients with ischemic heart disease. The results are summarized in Table 3. The results to date can be considered positive in a limited sense. Three of the studies found circulating platelet aggregates in the peripheral venous blood only of patients soon after myocardial infarction, (W2,W6,M13) and in the study by Drs. Willerson and Guyton at Parkland (W6) that was restricted to patients with transmural infarction. A recent work from Nashville also found circulating platelet aggregates in patients

TABLE 3.

ABNORMAL NUMBERS OF CIRCULATING PLATELET AGGREGATES
IN PATIENTS WITH ATHEROSCLEROTIC HEART DISEASE

Study	Year	Ref#	Results	
Wu & Hoak	1974	W2	+	Only in acute phase of MI
Willerson & Guyton	1977	W6	+	Only with acute transmural MI
Mehta, *et al*	1979	M13	+	Only soon after MI
Schwartz, *et al*	1980	S16	+	Only with acute MI and unstable angina pectoris
Serneri, *et al*	1981	S21	+	Stable angina, unstable angina, and remote MI

TABLE 4.

ABNORMAL PLATELET SURVIVAL IN PATIENTS WITH ATHEROSCLEROTIC HEART DISEASE

Study	Year	Ref #	Results
Murphy & Mustard	1962	M10	+
Abrahamsen	1968	A2	0
Salky & Dugdale	1973	S11	+
Steele, *et al*	1973	S12	+
Steele, *et al*	1975	S9	+
Ritchie & Harker	1977	R4	+
Steele & Rainwater	1978	S13	+
Steele & Rainwater	1980	S14	+
Doyle, *et al*	1980	D7	+
Fuster, *et al*	1981	F3	+

with unstable angina pectoris as well as patients with MI, but they, too, did not find circulating platelet aggregates in patients with stable angina pectoris or remote MI. (S16) Only the most recent study, from Italy, found significant circulating platelet aggregates in patients with more stable forms of ischemic heart disease. (S21)

Increased numbers of circulating platelet aggregates in peripheral venous blood following exercise-induced ischemia has been reported. Similar exercise did not lead to increased circulating platelet aggregates in normal controls. (K1)

Platelet survival

Platelet survival and turnover *in vivo* may be measured by determination of the decline of blood radioactivity following injection of autologous platelets that have been labeled *in vitro* with ^{51}Cr or ^{111}In or other radionuclides. (S3) A non-radionuclide technique has also been suggested based on recovery of the ability of platelets to generate thromboxane following permanent inhibition of platelet thromboxane synthesis of a cohort of platelets with aspirin administration. (S4) In a sense, survival determination may be considered the closest thing to a "gold standard" now available for estimation of *in vivo* platelet reactivity, but the technique is difficult to perform with accuracy and reproducibility. The results of platelet survival studies in patients with ischemic heart disease are outlined on table 4. The mean platelet survival of patients with ischemic heart disease was not always significantly shortened in these studies, but in all of the studies over half of the patients with ischemic heart disease had shorter platelet survival than normal controls.

Radioimmunoassay of platelet-specific proteins and Thromboxane B_2

The development of sensitive assays for the platelet-specific proteins platelet factor 4 (PF-4) and β-thromboglobulin (β-TG) and thromboxane B_2 are exciting recent developments that may have great promise in detecting abnormal states of *in vivo* platelet reactivity. While the use of these assays to detect platelet abnormalities in atherosclerotic processes may be more problematic than with disorders associated with major platelet destruction, there is reason to be hopeful that these assays will add to out ability to study platelet function in patients with atherosclerosis.

Platelet factor 4, a platelet specific protein (MW7800 daltons) with heparin neutralizing properties, is released during the platelet release reaction. Platelet factor-4 levels in platelet-poor plasma appear to be a marker for platelet reactivity *in vivo*. (S3) A sensitive radioimmunoassay has been developed. (H3,B3) Its half life in blood is very short (seconds or minutes). (D4)

A platelet-specific β-globulin was first described two decades ago. (S5,S6) It was later found to be located in the granules. (N3,D2,D3) It has been identified, purified, and characterized recently and given the name β-thromboglobulin by Moore, *et al.*(M6,M7) It is a basic protein with molecular weight of about 36,000 daltons, relatively chemically inert, and it comprises a major fraction of the total protein of platelet α granules. While the function of β-thromboglobulin remains obscure, Moore *et al* (M7) have suggested that it may be a

matrix or packing protein, helping to stabilize the active constituents of the α granules. Ludlam *et al* (L1,B4) developed a sensitive radioimmunoassay for β-thromboglobulin. Use of the radioimmunoassay has confirmed the specificity of β-thromboglobulin to platelets.(L2) Increased plasma levels of β-thromboglobulin have been documented recently during circumstances of platelet utilization (L3,O1,R1,S7,B5) and other disease states thought to be a result of platelet activation. (B6,C4,P1) The plasma half-life of β-thromboglobulin is much longer (∿ 100 min.) than that of platelet-factor 4. (D4)

While there is minimal prostaglandin synthesis in platelets, there is substantial generation of thromboxane A_2. Its generation potentiates collagen- and thrombin-induced platelet aggregation and may be essential for ADP- and epinephrine-induced platelet aggregation. Thromboxane A_2 is unstable *in vivo* (half life ∿ 31 seconds) but is converted to thromboxane B_2 which is much more stable in plasma. (S8) A radioimmunoassay has been developed in several laboratories recently, which is sensitive and has little cross-reactivity with prostaglandins and other arachidonic acid products.

The assays for PF-4, β-TG, and TxB_2 have been applied to studies of patients with ischemic heart disease only recently and many of the reports are available for review only in preliminary form. Most of these studies have some findings suggesting enhanced platelet reactivity in at least some of the patients. Several studies have examined the levels of these products in peripheral venous blood. The results of most of these studies are summarized in Table 5. It is much too early to come to a conclusion about these data at this early point on these studies. Nevertheless, available data with β-TG and PF-4 in patients with acute myocardial infarction and unstable angina pectoris appear to strongly favor abnormally enhanced platelet activity in some, but not all, of those patients. Results with patients with chronic stable angina are less convincing. The rather extraordinary elevations of TxB_2 in peripheral venous blood of patients with variant angina, especially soon after an episode of coronary spasm, are provocative, but additional data that I will review later suggest that if these elevations owe to platelet aggrevation *in vivo*, they may be a result of rather than a cause of the coronary artery spasm.

Dr. Paul Hirsh and his colleagues here recently reported the results of assay for TxB_2 of simultaneously drawn aortic and coronary sinus blood. (H11) The mean TxB_2 coronary sinus/aorta ratio was increased significantly only for patients with unstable angina pectoris who had experienced angina within 24 hours of study, but 3 of 18 patients with stable angina who had had angina 24-96 hours before study also had elevated values.

Use of β-TG, PF-4, and TxB_2 assays has been extended recently to assay of peripheral venous blood after exercise-induced ischemia and of simultaneously drawn arterial and coronary sinus blood after pacemaker-tachycardia-induced ischemia. Elevation of peripheral venous β-TG, (S23) PF-4, (G3) and TxB_2 (S27) following exercise-induced ischemia in some patients has been reported. Lewy *et al* (L6) found

TABLE 5.

ABNORMALLY ELEVATED β-TG, PF-4, and TxB_2 LEVELS IN PERIPHERAL VENOUS BLOOD IN PATIENTS WITH ISCHEMIC HEART DISEASE

Study	Year	Reference #	Stable Angina No Recent Pain	Stable Angina Recent Pain	Unstable Angina	Recent MI	Remote MI	Variant (Prinzmetal's) Angina	Comments
				β-TG					
O'Brien, *et al*	1977*	01				+			2 of 17 pts.
Denham, *et al*	1977*	D8				+			pts. with mur thrombus
Han, *et al*	1978*	H10							
Nichols, *et al*	1980*	N5	0				+		
Smitherman, *et al*	1981	S19	0		+	+			
Sobel, *et al*	1981	S20			+				only ≤ 12 hr after pain
Serneri, *et al*	1981	S21	+	+	+		+		
				PF-4					
Handin, *et al*	1978	H3	0		+	+			
Ellis, *et al*	1978*	E2	+		+	+			
Sobel, *et al*	1981	S20			+				only ≤ 12 h after pain
				TxB_2					
Lewy, *et al*	1979	L4						++	
Lewy, *et al*	1980	L5						++	
Sobel, *et al*	1981	S20			+				

0 = not elevated significantly
\+ = elevated values
++ = remarkably elevated values
* = preliminary report (abstract or letter to editor)

that tachycardia-induced ischemia led to increased TxB_2 in the coronary venous effluent in patients with recent unstable angina.

Do Patients with Atherosclerotic Heart Disease Have Enhanced Platelet Reactivity?

In light of the foregoing data, we can address the first of the questions that I posed at the outset of this review — Do patients with atherosclerotic heart disease have enhanced platelet reactivity? I think we can answer — Yes, almost certainly. The data are more convincing, however, during the syndromes of acute myocardial infarction and unstable angina pectoris than they are during chronic stable angina. It may be that enhanced platelet activity is of lesser importance during stable states with predictable, exertional angina than during the time of deterioration to an unstable state or myocardial infarction. These comments raise an equally or more important question, however, namely — Is the apparently enhanced platelet activity of some of these patients a cause or an effect of the complications of their disease? The answer to that question is not yet forthcoming and is a major issue for current and future investigation.

Drug alterations of platelet function.

A variety of drugs have been found to influence platelet function. Extensive reviews of this subject have been published recently. (P2,P5) These include (but are not limited to) aspirin, sulfinpyrazone, non-steroidal anti-inflammatory drugs, dipyridamole, β-adrenergic blocking agents, clofibrate, prostaglandins E_1, D_2, and I_2, heparin, cyproheptadine, glucocorticoids, vitamin E, furosemide, tricyclic antidepressants, phenothiazines, some anti-histamines, chloroquines, and the penicillin antibiotics, (W3,P2) It has recently been suggested that the slow-channel Ca^{+2} blocking drug verapamil may also alter platelet function. (R2) Those drugs with greatest relevance to the today's review are aspirin, sulfinpyrazone, the non-steroidal anti-inflammatory drugs, and dipyridamole and I shall limit my further comments to these drugs.

Aspirin

Aspirin does not appear to affect platelet adhesion to subendothelial substances. (B7,C5) However, it markedly inhibits collagen-induced platelet aggregation and the second wave of epinephrine- and ADP-induced platelet aggregation. It has very little effect on thrombin-induced aggregation. (P2) The anti-aggregatory effect is mediated through inhibition of thromboxane synthesis. Aspirin permanently acteylates platelet cyclo-oxygenase. Since new protein synthesis is virtually absent in the anuclear circulating platelets, a platelet thus affected is permanently altered. (R3, B8) This inhibitory action occurs at lower concentrations than are necessary to block PGI_2 production by vascular endothelium and smooth muscle. (B9) However, aspirin administration does not lengthen the platelet survival in patients with shortened platelet survival, (H4,H5) but does prolong the bleeding time. (Q1,W3,H6)

Sulfinpyrazone and Non-Steroidal Anti-inflammatory Drugs

Sulfinpyrazone is structurally related to phenylbutazone. Its anti-platelet effects appear to be similar to those of phenylbutazone and other non-steroidal anti-inflammatory drugs. These drugs block platelet cyclo-oxygenase, but not permanently. Sulfinpyrazone has an inhibitory effect on platelet aggregation *in vitro*, but in patients, even when administered in large doses, it has little or no effect on collagen-induced aggregation *in vitro* of platelets from these subjects. (W3) Sulfinpyrazone has a modest inhibitory effect on platelet adhesion *in vitro*. It lengthens platelet survival time in patients with shortened platelet survival, (S9,S10,W5,G1) but does not prolong bleeding time, (P2) opposite to the effects of aspirin.

Dipyridamole

Dipyridamole has an inhibitory action on platelet aggregation that has been more easily demonstrated with studies of circulating platelet aggregates than with *in vitro* platelet aggregation studies. (P2) From a variety of animal experiments, it can be inferred that dipyridamole inhibits platelet interaction with damaged vascular endothelium. (P2) This action appears to be mediated through inhibition of platelet phosphodiesterase with a consequent increase in platelet cAMP content. (M8) This action probably allows it to act as a potentiator of the effects of PGI_2 on platelets. (M9)

These are the three drugs that have undergone extensive clinical trials in patients with ischemic heart disease. Dipyridamole has generally been given in combination with aspirin. In reviewing the clinical trials with these antiplatelet agents, it is important to keep two basic but important reservations in mind: 1) these anti-platelet agents are only weak antithrombotic agents and affect only one aspect of thrombus formation; and 2) beneficial effects from these drugs could be due to drug actions in addition to or independent of their antiplatelet effects.

Epidemiologic Evidence for Antiplatelet Drug Efficacy in Patients with Ischemic Heart Disease

Since there was suggestive evidence for a role for platelets in complications of ischemic heart disease and since aspirin is so widely used, retrospective epidemiologic studies were undertaken in the early 1970's to look for a negative relationship of ischemic heart disease complications and regular aspirin use. The results were conflicting. The Boston Collaborative Drug Surveillance Group found a negative association between regular aspirin intake and non-fatal myocardial infarction in an analysis of drug intake of hospitalized patients, 776 with acute MI and 13,898 with other disorders.(B17). Hennekens *et al*, (H20) however, did not find such a negative association in a case — control study of 568 men who died from ischemic heart and 568 matched pairs. Although laborious, time-consuming, and expensive, it became clear that only prospective, randomized clinical trials could answer the question (F9) and at least 20 such trials have been initiated or planned.(P9)

Clinical Trials of Antiplatelet Drug Therapy In Patients With Atherosclerotic Heart Disease

Eight major secondary prevention trials of antiplatelet therapy with prospective randomized, placebo-controlled design have now reported their findings, four within the last year. (Table 6). I shall briefly outline the design, major findings, and major criticisms of each trial. (F7,G5)

TABLE 6

CHARACTERISTICS OF 8 CLINICAL TRIALS WITH PLATELET-ACTIVE DRUGS IN PATIENTS WITH ISCHEMIC HEART DISEASE

Trial	Acronym	Recruitment initiated	Follow-up completed
Elwood et al.	—	1971	1973
Coronary Drug Project Aspirin Study	CDPA	1972	1975
German-Austrian Multi-center Prospective Clinical Trial	—	1970	1977
Elwood and Williams	—	1976	1978
Aspirin Myocardial Infarction Study	AMIS	1975	1979
Elwood and Sweetnam	—	1975	1979
Persantine-Aspirin Re-Infarction Study	PARIS	1975	1979
Anturane Reinfarction Trial	ART	1975	1978

Trial	Drug	Total daily dose	Dosage schedule
Elwood et al.	ASA	300 mg	q.d.
CDPA	ASA	972 mg	t.i.d.
German-Austrian	ASA Phenprocoumon	1500 mg	t.i.d.
Elwood and Williams	ASA	300 mg	single dose
AMIS	ASA	1000 mg	b.i.d.
Elwood and Sweetnam	ASA	900 mg	t.i.d.
PARIS	ASA ASA + dipyridamole	972 mg 972 + 225 mg	t.i.d.
ART	Sulfinpyrazone	800 mg	q.i.d.

Abbreviation: ASA = acetylsalicylic acid (aspirin).

Continued on next page.

TABLE 6 (Continued)

CHARACTERISTICS OF 8 CLINICAL TRIALS WITH
PLATELET-ACTIVE DRUGS IN PATIENTS WITH ISCHEMIC HEART DISEASE

Trial	No. of pts randomized	No. of pts excluded	No. of pts analyzed	Sex	Mean age (years)
Elwood et al.	1239	0	1239	M	55.0
CDPA	1529	0	1529	M	56.5
German-Austrian	1060	114	946 (626)*	M & F	58.9
Elwood and Williams	2530	825	1705	M & F	
AMIS	4524	0	4524	M & F	54.8
Elwood and Sweetnam	1725	43	1682	M & F	56.2
PARIS	2026	0	2026	M & F	56.3
ART	1629	71	1558	M & F	56.6

*Aspirin and placebo groups only.

Trial	Primary response variable	Secondary response variable
Elwood et al.	Total mortality	—
CDPA	Total mortality	Coronary death, nonfatal MI, other CV events
German-Austrian	SD and fatal and nonfatal MI	—
Elwood and Williams	Total mortality	—
AMIS	Total mortality	CHD mortality, CHD incidence, stroke
Elwood and Sweetnam	Total mortality	—
PARIS	Total mortality, coronary mortality, coronary incidence	Nonfatal cardiovascular events
ART	Cardiac mortality	—

Abbreviations: SD = sudden death; CHD = coronary heart disease; CV = cardiovascular.

M.R.C. Epidemiology Unit (Elwood *et al*)
Aspirin Study - I (1971-1973)*

This trial was carried out in 5 centers in Great Britain. (E3,E6) It was a trial of aspirin, 300mg once a day. A total of 1239 men with recent myocardial infarction were enrolled. The mean time between MI and enrollment was 10 weeks; almost 50% of the patients were enrolled

* (Year recruitment initiated - year followup completed)

within 4 weeks of MI. One hundred and thirteen patients dropped out but analysis was based on all patients. (It is a major tenet among many clinical trial biometricians that all randomized patients should be included in the data analysis, regardless if they remained in the trial or not). All-cause mortality was reduced by 25% (8.3% *vs* 10.9%) in the aspirin group one year after infarction. The one year reduction was twice the reduction at 6 months. This result did not achieve statistical significance ($p>0.05$ by t test). This study has been critized for 2 reasons: 1) there were major differences in outcome among the 5 centers. Most of the benefit was seen in only one center (Cardiff, Wales) at which 1/2 the total number of patients were enrolled; and 2) slightly more than half the patients were enrolled more than 4 weeks after MI. (Since the death rate falls more or less exponentially after MI, some experts in this area felt that survivors of MI should be entered into trials of this sort early rather than later to maximize the chances of seeing any drug treatment effects.)

Coronary Drug Project Aspirin Study (CDPA) (1972-1975)

This trial was carried out in 53 clinical centers. (C6,C7) It was a double blind, randomized, placebo-controlled trial of aspirin, 324mg three times daily (972mg/day). A total of 1529 men with previous MI were randomized and data from all patients were analyzed. Patients were followed 10-28 months (average = 22 months). The aspirin group had 30% fewer deaths than the placebo group (5.8% *vs* 8.3%, $Z = -1.90$). The greatest difference in mortality was at 24 months ($Z = 2.61$). Coronary death was 27% lower in the aspirin group (4.6% *vs* 6.4%, $Z = -1.49$) and sudden death was 19% lower in the aspirin group (2.6% *vs* 3.2%, $Z = -0.70$). The incidence of non-fatal MI was only slightly lower ($Z = -0.48$) in the aspirin group. The most impressive difference between aspirin and placebo for combinations of various fatal and non-fatal cardiovascular events was the combination of coronary death or definite non-fatal MI. The aspirin group was 21% lower than the placebo group (8.0% *vs* 10.2%, $Z = -1.49$). (None of these differences attained statistical significance according to the rigorous criterion of a Z value of 2.6, which roughly corresponds to a p value < 0.01. A Z value of 1.98 roughly corresponds to a p value < 0.05. This rigorous criterion is often set in these clinical trials because the data are examined on multiple occasions, not just once at the end.) These investigators interpreted the study cautiously as showing a trend for an aspirin benefit.

This study has been criticized because they chose a high dose of aspirin. Of course this study and the others that I will review this morning were commenced long before the unfolding of the thromboxane A_2 - prostacycline story. It has also been criticized because most of the men were enrolled long after their most recent MI and were in a low-risk period of their disease.

German-Austrian Multicenter Prospective Clinical Trial (1970-1977)

This trial was carried out in 7 centers in Germany and Austria. (B18, B19) A total of 626 men and women with MI 30-42 days before were randomized to either placebo or aspirin, 500mg t.i.d. Another

316 patients were allocated to a group treated with an oral coumarin anticoagulant. Compared to placebo, total mortality was reduced by 26.1% in the aspirin group (Z = 0.79), coronary deaths were reduced by 42.3% (Z = 1.64), sudden deaths were reduced by 36%, non-fatal myocardial infarctions were reduced by 27% and coronary events (coronary death + non-fatal acute MI) were reduced by 20% (Z = 1.86, p~0.06). None of these changes attained statistical significance.

The major criticisms of this trial are: 1) that almost half the patients dropped out or were lost to followup and their status at the end of the study period was unknown; and 2) the high dose of aspirin.

M.R.C. Epidemiology Unit (Elwood & Williams)
Aspirin Study - II (1976-1978)

This trial was carried out in 12 hospitals in South Wales. (E5,E6) A total of 1725 men and women were enrolled as soon as possible after the diagnosis of MI was confirmed. Twenty-five percent were enrolled within 3 days of the MI and 99% were enrolled within 20 days. They were randomized to aspirin 300mg t.i.d. (900mg daily) or placebo and followed for one year. Overall mortality was decreased, but insignificantly so ($p>0.05$), in the aspirin group by 17.3% (12.3% *vs* 14.8%). Data on non-fatal infarction were incomplete. Several criticisms have been raised: 1) twenty six percent of the randomized patients were withdrawn from treatment; 2) the large number of patients admitted to the study within one week of MI may have diluted the results since some deaths at that stage after MI, e.g. pump-failure deaths, would probably not be influenced by aspirin; 3) follow-up data except as to life or death are incomplete; and 4) the high dose of aspirin.

Aspirin Myocardial Infarction Study (AMIS) (1975-1979)

This trial was carried out in 30 centers in the United States. (A5,A6) A total of 4524 men and women were randomized to aspirin, 0.5g b.i.d. (1.0g daily) or placebo. They were randomized 2-60 (average = 25) months after the last MI. They were followed for a minimum of 3 years. The size of the study was deliberate - the hope was that this would be the definitive study.

The 3-year overall mortality was slightly and insignificantly higher in the aspirin group (9.6 *vs* 8.8%). The incidence of both coronary death and sudden death were slightly and insignificantly higher in the aspirin group. The incidence of recurrent non-fatal MI was reduced 22% and coronary incidence (coronary mortality + non-fatal MI) was insignificantly reduced by 4.7% (14.1 *vs* 14.8%) in the aspirin group. In spite of the 22% reduction in incidence of recurrent MI, the investigators interpreted their study as being completely negative for a benefit of aspirin.

This study has been criticized for: 1) the long period between last MI and randomization; 2) the high dose of aspirin; and 3) the totally negative interpretation they gave their data in spite of the reduction in the incidence of recurrent MI.

M.R.C. Epidemiology Unit (Elwood and Sweetnam)
Aspirin Study - III (1975-1979).

This trial was carried out by 3000 general practioners under the guidance of the M.R.C. Epidemiology Unit. (E4,E6) It is quite different from the other 7 trials available for comparison. It was a placebo-controlled, randomized trial of a single 300mg dose of aspirin upon first contact with a patient with suspected MI. All were given the medicine within 24 hours; 70% received it within 4 hours of the onset of symptoms. A total of 2350 men and women were enrolled. Death within one month of infarction was analyzed and was almost identical in the 2 groups (19.2% ASA, 19.6% placebo). The major criticisms of this study are: 1) the uncertainty of the final diagnosis of the patients; and 2) the use of only a single dose of aspirin; and 3) administration of aspirin so early after MI.

Persantine-Aspirin Re-Infarction Study (PARIS) (1975-1979)

This trial was carried out at 16 American and four British clinical centers. (P6,P7,P8) A total of 2026 men and women were randomized to placebo, aspirin 325 mgm t.i.d. (975mg daily), or the same dose of aspirin + 75mg Persantine (dipyridamole) t.i.d. There were twice as many patients in each drug group as in the placebo group by design because this study was carried out concurrently with the AMIS trial and was planned initially more to compare the two drug regimens than with placebo. Patients were enrolled after MI from the time of hospital discharge to 60 months. Patients were followed for up to 4 years (average = 41 months).

Overall mortality was reduced by 16% by Persantine + aspirin ($Z = 1.00$) and 18% by aspirin ($Z = 1.06$) compared to placebo; coronary mortality was 24% ($Z = -1.32$) and 21% lower ($Z = -1.01$) respectively. Persantine + aspirin decreased sudden death rate 29%, but aspirin raised the sudden death rate 27%. Coronary incidence (coronary death + non-fatal MI) was reduced 25% ($Z = -2.30$) by Persantine + aspirin and 24% ($Z = -2.18$) by aspirin. Note that coronary incidence did not achieve the rigorous Z level of 2.6 ($p<0.01$) but did surpass $Z = 1.98$ ($p<0.05$). Non-fatal myocardial infarction was insignificantly decreased by both aspirin + Persantine (20%, $Z = -1.54$) and aspirin (30%, $Z = -2.11$).

When the PARIs group re-analyzed their data limited to the small number patients enrolled within 6 months of MI (~ 20% of total), the apparent effects of both Persantine + aspirin and aspirin were more impressive. For those patients, total mortality was reduced by 44% for aspirin + Persantine ($Z = -1.59$) and by 51% for aspirin ($Z = -1.64$) and accounted for much of the reduction in mortality of the total group. On the other hand, the effect on reducing recurrence of MI was seen chiefly in the group of patients randomized $\geq$ 6 months after MI.

For the whole group, Persantine + aspirin and aspirin were most effective for the time period 8-24 months after beginning therapy. The Z value was $\geq$ 2.6 at all time points from 8-24 months for Persantine + aspirin and for 2 time points for aspirin.

This group interpreted their findings very cautiously as showing only a strong trend favoring both Persantine + aspirin and aspirin. They are beginning a new trial, PARIS-II, which is similar in design but the intake window after MI will be narrower. The dose of aspirin will be the same.

This study has been criticized for: 1) the long interval between last MI and enrollment; 2) the inequality in the size of the study and placebo groups; and 3) the dose of aspirin.

Anturane Reinfarction Trial (ART) (1975-1978)

This trial was carried out at 21 centers in the United States and 5 in Canada. (A3,A4,S24) A total of 1558 men and women were randomized to Anturane (sulfinpyrazone) 200mg QID or placebo 25-35 days after MI. They were followed for 1-2 years. Four hundred and fifteen patients withdrew prematurely.

The incidence of analyzable cardiac death was reduced by 32% ($p = 0.058$) by sulfinpyrazone; the incidence of analyzable sudden death was reduced by 43% ($p = 0.041$). This was most marked in the first 6 months, during which the analyzable sudden death rate was reduced by 74% ($p = 0.003$).

This study created considerable interest and controversy. It was criticized because: 1) deaths that were from inelgible patients and those that were "non-analyzable" (deaths at a time when drug administered for < 7 days or > 7 days after drug withdrawal) were not included in the original data analyses; 2) not all data were tabulated in the publications precluding a complete, independent data analysis; 3) mode of death stratification was felt to be imprecise; 4) the report came to an enthusthiastically positive conclusion regarding sulfinpyrazone efficacy although the only variable that achieved statistical significance at the 1% level was one subgroup analysis.

An Overview Of The Clinical Trials

The results and interpretations of these clinical trials has set off what has been referred to, only partly in jest, as a biostatistical cold war. This was triggered by the different techniques used in data analysis in the studies, by the interpretations each study group gave their own data, negative for AMIS, very cautiously positive for PARIS, enthusiastically positive for ART, and the subsequent application for and denial of FDA approved indication status for sulfinpyrazone in the post-MI period. (K2,R11,T1,M22) We cannot resolve those issues this morning.

Nevertheless, if we look at all the results from these trials at one time, I think that it is fair to be cautiously optimistic that antiplatelet therapy does decrease the likelihood of complications of ischemic heart disease. The % reduction of mortality, sudden death, and non-fatal myocardial infarction of all studies are outlined on table 7 and are illustrated in figs. 1 and 2. Mortality was decreased in 7 of 8 regimens in the 7 long-term trials, sudden death was decreased in 4 of the 6 in which it was reported separately, and non-fatal MI was decreased by all of the 7 regimens in the 6 studies in which it was reported. But when these data are all analyzed independently by the same technique, only three of these results are significant at the 5% confidence level, non-fatal MI in the AMIS and the second M.R.C. trial (Elwood and Sweetnam) and sudden death in the Anturane Reinfarction Trial.(F7)

TABLE 7 *Post-Myocardial Infarction Treatment in Randomized Trials*

Trial	Drug	Dose	No. of patients	% Reduction (treated vs control)		
				Mortality	Sudden death	Myocardial infarction (Nonfatal)
Elwood I	Aspirin	300	1239	24	—	—
CDPA	Aspirin	972	1529	30	19	5
German-Austrian	Aspirin	1500	1060	18	36	27
AMIS	Aspirin	1000	4524	+11	+35	22*
Elwood II	Aspirin	900	1725	17	—	35*
PARIS	Aspirin	972	2026	18	+27	29
	Aspirin + dipyridamole	972/ 225		16	16	19
ART	Sulfinpyrazone	800	1629	30	43*	25

*$p > 2$ standard errors of the difference.

Abbreviations: CDPA = Coronary Drug Project Aspirin; AMIS = Aspirin Myocardial Infarction Trial; PARIS = Persantine-Aspirin Reinfarction Study; ART = Anturane Reinfarction Trial.

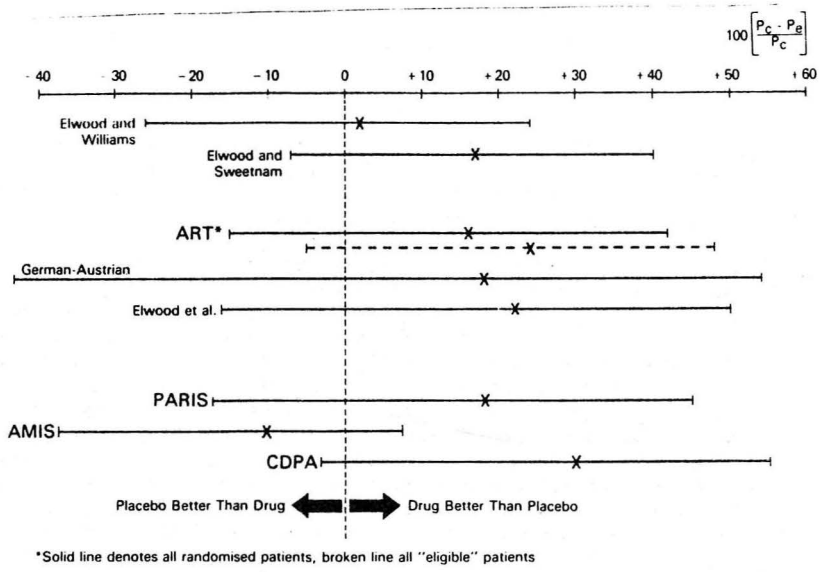

FIGURE 1. *Estimates (X) with 95% confidence intervals of the relative difference in all-cause mortality between placebo (P_c) and platelet-active drug (P_e) in eight trials of post-myocardial infarction patients. (Courtesy of Furberg CF, May G, Wedel H.)*

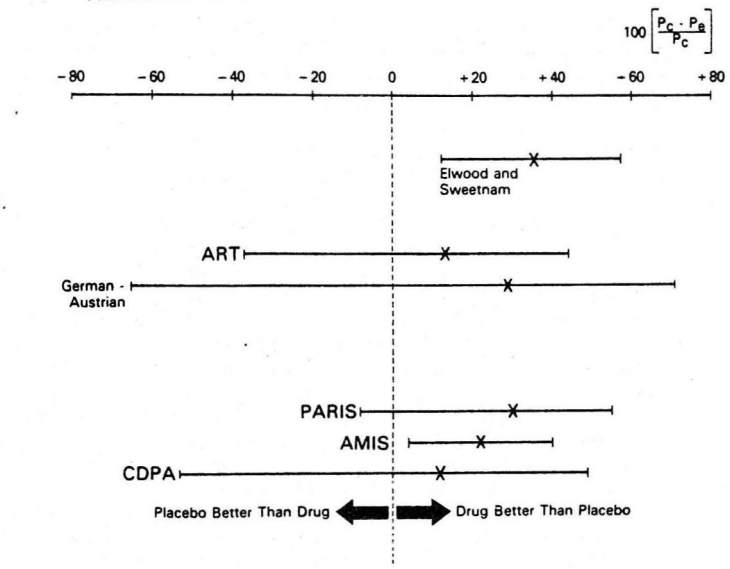

Figure 2. Estimates (X) with 95% confidence intervals of the relative difference in incidence of nonfatal myocardial infarction between placebo (P_e) and platelet-active drug (P_e) in six trials of post-myocardial infarction patients. (Courtesy of Furberg CF, May G, Wedel H.)

With these results in mind, we can address the question - can platelet-active drugs decrease the incidence of complications of some of these patients? I think the best answer is - yes, possibly. More results will be necessary to strengthen that conclusion and more results will be available soon.(P9) Fortunately some of those studies are testing patients at fairly high risk for coronary events. The results of the VA Coop Study of Aspirin in Unstable Angina will be available in the spring of next year. PARIS - II will examine only patients with fairly recent MI.

It is important to keep in mind some reservations about the use of platelet-active drugs in managing patients with ischemic heart disease. Aspirin does not change the threshold for stable exertional angina.(D9,F2) Aspirin and indomethacin effectively prevent production of thromboxane in the coronary circulation of patients with Prinzmetal's angina without diminishing the frequency of episodes of pain or ST-segment elevation.(R10,C9) Indeed these data suggest that platelet activation in patients with Prinzmetal's angina may be the result of instead of the cause of coronary spasm in these patients.

The Current Role For Antiplatelet Therapy In Patients With Ischemic Heart Disease

The last of the three questions to be addressed this morning is the hardest to answer - what is the proper role for platelet-active drug therapy for these patients today, given our current state of knowledge? For the time being, physicians will have to make their own best-possible decisions regarding the specific problems of each patient. Nevertheless, I think that a few general recommendations can be made. I do not think that current knowledge supports the routine administration of platelet-active drugs either to prevent development of atherosclerosis or to prevent complications with established, stable atherosclerotic heart disease. I think that a fairly good case can be made for antiplatelet drugs during high-risk periods of a patient's course e.g. the first six months after survival from MI, during and for several months after unstable angina pectoris, and for several months after the new onset of angina.

Definitive recommendations of specific drug regimens are also very difficult based on current knowledge, but the results with sulfinpyrazone and aspirin + dipyridamole appear to be the most promising. But what aspirin dose? Low-dose ($\leq$ 325mg/day) or high-dose ($\geq$ 650mg/day)? We have only intuition to guide us. Recent literature suggests that low-dose aspirin may be more appropriate as an anti-platelet regimen than high-dose aspirin owing to differential effects on the cyclo-oxygenase systems of endothelium and platelets, but that debate is unresolved.(S25) Furthermore, high-dose aspirin was associated with substantial patient intolerance and side effects in all studies. Yet, with one exception, the clinical trials were carried

out with high-dose aspirin and it may not be appropriate to extrapolate the expected results from high-dose to low-dose aspirin treatment. I favor low-dose aspirin since demonstrable *in vitro* and *ex vivo* anti-platelet effects are maximal or nearly so with low-dose aspirin and since long-term, high-dose aspirin is so poorly tolerated.

At this juncture, I would also recommend that anti-platelet therapy for ischemic heart disease be limited principally to men. After the beneficial effects of antiplatelet therapy after hip surgery (H19) and in patients with transient cerebrovascular ischemia (C8,G6,F8) were found to be limited mostly to men, most of the clinical trials that I have reviewed reanalyzed their data. Since ischemic heart disease is rarer in women than men, the numbers studied were small, but the same sex differential effects appear to be present in these studies.(G5)

All these recommendations are tentative. Future knowledge will likely change them. We should adhere to Pasteur's injuction, "Keep your enthusiasm, but let strict verification be its constant companion".

Other agents, especially β-adrenergic blocking drugs and classical anti-arrhythmic drugs, may also be protective against deaths in patients with ischemic heart disease during high-risk periods. These drugs are currently being investigated in several clinical trials. Bear in mind that we do not now know if the effects of these agents are additive or not. It may be that all these agents spare the same patients.

A Look To The Future

The future for new information in this area looks bright in addition to the anticipated results from other clinical trials with cyclo-oxygenase inhibitors and dipyridamole. Measurement of blood products of platelet aggregation and granule release may provide us with the tools to more rationally choose patient subgroups for antiplatelet therapy. The recent availability for intravenous infusion of the vasodilator and anti-aggregatory prostaglandins PGE_1 and PGI_2 will now allow careful testing of the effects of this powerful mode of antiplatelet therapy of patients with ischemic heart disease. Its use in acute ischemic syndromes is particularly attractive.(B21) Finally, development of new drugs with more selective effects on platelets and endothelium appears quite promising.

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