

Editorial

Aspirin, Platelets, and Bleeding

RECENT findings regarding the effect of acetylsalicylic acid on platelet function provide an interesting example of how astute clinical observation can lead to the discovery of basic physiologic and pathologic mechanisms. For many years Dr. Armand Quick had suspected that the ingestion of aspirin by hemophiliacs exaggerated their bleeding diathesis. We were interested to find that some of the ear, nose, and throat surgeons in our institution forbade patients' taking aspirin before an operation because they have associated its administration with increased bleeding at operation. The most impressive clinical evidence that aspirin causes bleeding, however, comes from its relationship to gastrointestinal bleeding.

There are now many reports that the administration of aspirin causes occult gastrointestinal bleeding and, despite a few claims to the contrary, the evidence seems quite convincing. Blood loss from the gastrointestinal tract can be detected in 70% of normal subjects after the administration of about 3 g of aspirin, and overt hemorrhage may occur. A local irritative effect on the gastrointestinal mucosa has been suggested as the cause of bleeding. Such a local effect is not the entire explanation, however, because intravenous administration of salicylates also produces a slight increase in occult gastrointestinal blood loss. Other etiologic mechanisms have been postulated, including an allergic reaction, increased gastric acidity, a central effect, and a cortisone-like effect.

The clinical evidence that aspirin causes some derangement of the hemostatic mechanism is most suggestive and is supported by a number of experimental observations that seem to have been largely ignored until recent years. Salicylic acid and sodium salicylate cause a slight prolongation of the one-stage prothrombin time in rats maintained on a diet

low in vitamin K. In humans, acetylsalicylic acid and sodium salicylate in doses of 1.3 to 5.3 g daily cause a similar mild lengthening of the prothrombin time, which is prevented by administration of vitamin K. The aspirin must be given for several days to prolong the prothrombin time for 1 to 2 seconds, and small doses of aspirin cause no detectable effect. It seems unlikely that the hemostatic abnormality produced by small doses of aspirin is due to any pronounced effect on the coagulation mechanism. Indeed, Quick described these findings as a "veritable red herring."¹

Because the plasmatic coagulation mechanism did not seem to be a fruitful area for research, interest returned to the observation, made more than 10 years ago by Beaumont and colleagues and by Frick, that aspirin prolongs the bleeding time. Other workers have made similar observations, but their findings were overlooked until Quick's recent work¹ on the subject stimulated further investigation. Quick found that more than half of a group of normal subjects showed a small but significant increase of the Duke bleeding time 2 hours after ingestion of 1.3 g of aspirin. Even more sensitive were patients with von Willebrand's disease: They had prolongation of the bleeding time after 0.65 g (2 tablets) of aspirin.

In recent years, research on the blood platelet has undergone a renaissance, and current investigations suggest that aspirin's effect on the bleeding time and on hemostasis may be due to a direct effect on platelet function. According to current concepts, the primary defense against bleeding appears to be platelet plugging at the site of injury. First, platelets are attracted to the injured vessel, probably to collagen. Other platelets attach to the trapped platelets, and an effective hemostatic plug is soon formed. Only later do fibrin threads develop and add permanence to the plug.

One of the major advances in the physiology of hemostasis was the discovery that platelet clumping can be induced by adenosine diphosphate (ADP). It is believed that ADP is important in the living animal in that growth of the platelet plug depends on release of the ADP by platelets which have become adherent to the injured vessel wall. In vitro the aggregation of platelets by ADP is readily demonstrated by the change in transmittance of light passed through a tube of platelet-rich plasma. If the amount of ADP added is carefully adjusted, one can often see two waves of change of transmittance. This biphasic response is usually explained as follows: The added ADP causes some platelets to aggregate, permitting more light to pass through the tube; the aggregating platelets release endogenous ADP which causes further aggregation and increases the transmittance again (fig. 1). If one adds epinephrine, instead of ADP, to platelet-rich plasma, a two-phase aggregation is again observed. When thrombin or a suspension of collagen is added to platelet-rich plasma, only one wave of aggregation occurs, and it is somewhat delayed (fig. 2), so that these agents probably cause aggregation by inducing the platelets to release their ADP.

It has now been shown that, 2 hours after the ingestion of 1.3 g of aspirin or when aspirin is added to blood in vitro,² the release

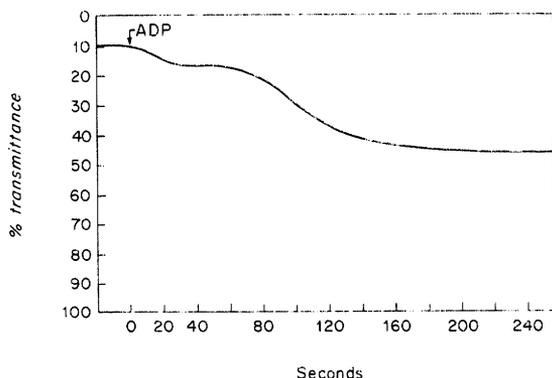


Figure 1

Aggregation of normal human platelets (platelet count, 420,000/cu mm of plasma) by ADP (final concentration, $10^{-7}M$), showing primary and secondary phases of aggregation.

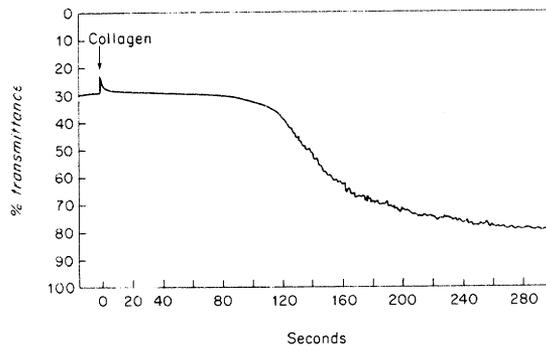


Figure 2

Aggregation of normal human platelets (platelet count, 420,000/cu mm of plasma) by saline extract of collagen, showing one phase of aggregation after initial delay.

of platelet ADP is blocked and the secondary phase of aggregation is inhibited.³⁻⁵ Similarly, the ability of collagen particles to induce platelet aggregation is impaired (fig. 3). Secondary aggregation induced by epinephrine is also blocked, as well as aggregation produced by antigen-antibody complexes,² γ -globulin-coated surfaces, and triethyl tin.⁴ Chlorpromazine, desmethylinipramine, and several drugs showing one or more of the properties of aspirin also inhibit the second phase of ADP-induced aggregation. Thrombin-induced aggregation has been reported by some to be normal after ingestion of aspirin, but other workers point out that, if small

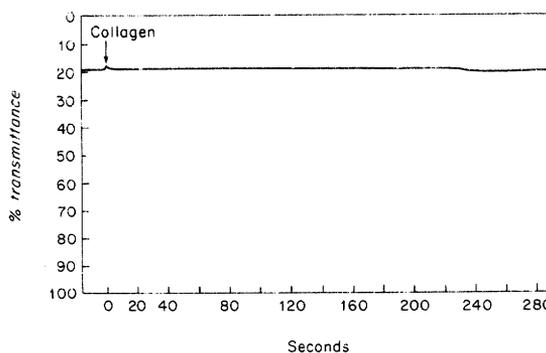


Figure 3

Inhibition of collagen-induced aggregation of platelets (platelet count, 571,000/cu mm of plasma) from normal human subject taking 650 mg of aspirin every 2 hours (control curve for same subject is shown in figure 2).

amounts of thrombin are used, aspirin is inhibitory.² It is of interest in this regard that sulfapyrazone and phenylbutazone block the aggregating action of collagen, antigen-antibody complexes, and γ -globulin-coated surfaces but not that of ADP or thrombin.

Most, but not all,² authors agree that the abnormality of platelet function is induced only by aspirin and not by sodium salicylate. Quick could not demonstrate any prolongation of bleeding time with sodium salicylate alone. He postulated that aspirin prolonged the bleeding time by depressing a plasma factor that controls bleeding from small vessels and that this action is determined by the acetyl group and not the salicylate moiety. The existence of such an aspirin-sensitive plasmatic factor has not been experimentally confirmed although the existence of "vascular" factors has been postulated and the absence of such a factor has been suggested as the cause of the long bleeding time in von Willebrand's disease.

The antihemostatic effect of aspirin has been found as long as a week after its ingestion, well after all traces of salicylates have disappeared from the peripheral blood. This suggests that aspirin permanently damages the platelets. In view of the fact that salicylates have been shown to affect the enzyme systems responsible for oxidative phosphorylation, dehydrogenases, and aminotransferases, it has been suggested that aspirin affects either some enzyme pathway in the platelet⁴ or membrane permeability.^{4, 5} It has been recently found that aspirin inhibits platelet glycolysis, perhaps as a result of inhibition of glucose transport across the platelet membrane, although it seems that the inhibition of ADP release on exposure to collagen is mediated by a different mechanism.⁶ Further evidence of a membrane effect is provided by experiments using ¹⁴C-labeled aspirin. When the acetyl group was labeled, platelet radioactivity was detected only in membrane-subcellular or granule-subcellular fractions. It is of interest that no radioactivity was detectable in the platelet when the carboxyl group was labeled.⁷

In recent years a disease has been described in which the interaction between platelets and collagen is abnormal; when collagen extracts or particles are added to the platelets from these patients, virtually no aggregation occurs. The inhibitory effect of aspirin and other drugs on platelet aggregation makes it important to obtain a careful drug history before interpreting platelet-aggregating tests because some of the patients reported as having an abnormality of collagen-induced aggregation could have been taking aspirin. However, we have studied one patient who had defective collagen-induced aggregation of platelets but was not taking aspirin or other drugs. Recently, aspirin has been found to inhibit release of the heparin-inhibiting activity (platelet factor 4) of platelet.⁸

Current studies are important in elucidating the role of platelets in hemostasis because they contribute to our knowledge of platelet physiology and have been the stimulus for much related research. Furthermore, it is quite possible that aspirin might be useful therapeutically in conditions which predispose to thromboembolism. The clinical significance of these findings, however, requires additional critical evaluation and some skepticism. Not too long ago it was thought that the effect of aspirin on hemostasis was exerted on the clotting mechanism. Now it seems more likely that its effect on platelets is of greater functional importance. But aspirin has such widespread metabolic effects that it seems quite probable that further work may reveal still other effects, perhaps on the blood vessel directly or on some other anti-bleeding factor that has not yet been discovered.

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The Medical School Predictions of a Dean Utopia or the Inferno

. . . the medical schools will be even more altered. It will, I believe, be possible for a student to enter regardless of his age or specific undergraduate credits, if he can pass a qualifying examination in bioscience. I hope, but cannot be certain, that he will also have to demonstrate at least reasonable competence in the use of English, something which many present day students do not possess. If I had my way, there would also be a requirement having to do with the study of the successes and failures of political and social action in the past, whether one called it history or not. The medical school itself will be hardly recognizable as a separate academic entity; it will be closely integrated if not totally merged with its parent university. The student will be able to proceed to his qualifying degree at his own pace; some may take five or six years to get there, others two or three. Gone will be today's preclinical and clinical compartments. There may be no departments as such. From the first, the student will receive clinical exposure, bolstered by and interlarded with relevant basic science topics. Much of his teaching will be via the use of self-learning devices and when he finds, by such means, that he has attained a certain level of understanding, he will be admitted to a single final examination.

He will have learned very little technical medicine—virtually no operative surgery, for example—and his clinical exposure will have been in a carefully regulated mixture of environments: a large medical center, a small community health unit, and possibly as a sort of apprentice to a group practice organization. He will not, on receiving his degree, be qualified to practice. That will require a two-year clinical exposure, considerably more standard but better planned than most of today's internship, which will be run by the medical school in association with hospitals. Highly specialized training will begin, for those who want it, at some point in the two-year internship phase and those opting for basic science will go an entirely different route, branching off somewhere during the medical school phase.—FROM CARLETON B. CHAPMAN: *Politics and the health professions: With special reference to medical education*. *Pharos* **32**:73, 1969.

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