Platelets were discovered by G. Bizzozero in 1882 and rediscovered in the 1960s after many decades of oblivion. Interestingly enough, their role was initially more clearly associated with thrombosis than with hemostasis. For many years a serious unresolved problem was that the clotting time was normal even in severe thrombocytopenia. The concept of coagulation as an enzymatic cascade had not yet been elaborated. During the 1960s, the interest of many experts moved from the interaction of platelets with the process of blood coagulation to the interaction of these cells with the vascular wall (adhesion) and each other (aggregation). The discovery of the role of ADP as the principle of platelet aggregation stimuli was rapidly followed by other important discoveries such as the aggregating properties of collagen and thrombin, the release reaction, the metabolism of arachidonic acid, and the inhibitory effect of aspirin. The use of aspirin as a potential antithrombotic drug has made the history of clinical trials in the last 30 years. The last two decades have been characterized by an explosion of cell and molecular biology approaches. There are presently people who study platelet signal transduction or platelet-leukocyte interactions but who know almost nothing about hemostasis or thrombosis! This is due not only to the intrinsic limitations of the biological approach but also to the progressive recognition of the role of platelets in other physiopathologic and clinical conditions such as inflammation, cancer growth and dissemination, and organ transplant rejection. Overlooked for more than two centuries after the microscope was made available to hematologists, considered as an artifact or a Cinderella, the platelet has mainly been considered in the past 30 years as a dangerous cell to be inhibited by (ever more expensive) drugs. But the taming of the shrew is far from being achieved.

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Key words: platelets, hemostasis, thrombosis, history
Both Bizzozero and Hayem presented evidence that platelets (or hematoblasts) participate in the early phase of blood coagulation, as they observed that fibrin strands appear at loci where platelets adhere and undergo morphologic changes. The more rapid coagulation of blood, flowing from a wound which had been open for some time, is probably due to the presence of aggregates of blood platelets which have formed after the time of the first incision, on the surface of vascular lesions and the margins of incision.\textsuperscript{1,3} Both investigators concluded that platelets supply a factor needed in the clotting reaction. However, the observation that the clotting time was normal even in severe thrombocytopenia led many other investigators to conclude that platelets are not necessary in the coagulation of blood\textsuperscript{4} although Roskam\textsuperscript{6} had already described in 1923 the presence of fibrinogen on the platelet surface, suggesting that the fibrinogen-fibrin transition on the platelet surface might be of importance. According to Quick,\textsuperscript{7} it was his prothrombin consumption time test that supplied a clear answer to the role of platelets in coagulation. This procedure, indeed, showed that even when the clotting time is normal, the prothrombin consumption is markedly reduced when normal plasma depleted of platelets is clotted. Mixed experiments with platelet-poor normal plasma and platelet-rich plasma from patients with hemophilia A suggested that a clotting principle in platelets (surface phospholipids) reacting with a plasma factor lacking in hemophilia (factor VIII) accelerates the intrinsic coagulation process.

From Cinderella to royal prominence

Despite the excellency of these and other contributions, the platelet remained for many years the neglected stepchild in the family of blood cells. Finally, around 1960, the platelet emerged from the Cinderella stage to that of royal prominence.\textsuperscript{8} The work by Hugues and Bounameaux in Roskam’s group in Liège\textsuperscript{9} showed that the collagen component of connective tissue leads to platelet adhesion and aggregation culminating in viscous metamorphosis. Some other important discoveries were made at about the same time: the isolation and description of a contractile protein resembling actomyosin in platelets,\textsuperscript{10} and the recognition that adenosine-5’-diphosphate (ADP) is a potent inducer of platelet aggregation.\textsuperscript{11}

This latter finding was originally based on the liberation of platelet aggregating material from red cells (factor R of Hellem).\textsuperscript{12} This only attained its full significance with the observation that platelets themselves, under the influence of a suitable agent such as thrombin, release enough of this dinucleotide to induce their own aggregation.\textsuperscript{13} The recognition of this phenomenon remains a most important step in the understanding of the mechanism of platelet aggregation, which accordingly appeared as a self-perpetuating process.\textsuperscript{14} In the early sixties, Born and Cross\textsuperscript{15} and O’Brien\textsuperscript{16} described an optical platelet aggregation test, roughly based on the decrease of optical density of a platelet suspension corresponding to platelet clump formation by a given stimulus. Very soon, this appeared to be an easy and practical method and platelet aggregation could be studied in dozens of laboratories all around the world. Now, about 40 years later, the molecular basis of ADP-induced platelet activation is only beginning to be understood and a model of three purinergic receptors, each contributing separately to ADP-induced mechanisms has been proposed.\textsuperscript{17}

Meeting with aspirin

In the years 1967–1968, aspirin and the platelet met each other officially for the first time and a never-ending story was begun. In reality, already in the fifties French investigators\textsuperscript{18,19} had observed that aspirin, in relatively small doses, resulted in a prolongation of bleeding time. They also noted that this effect was exaggerated in patients who had underlying bleeding disorders. These clinical observations were confirmed in the USA by Quick\textsuperscript{20} who also made the important observation that, unlike aspirin, sodium salicylate had no effect on bleeding time. Weiss and Aledort\textsuperscript{21} first showed that prolongation of the bleeding time by aspirin (3 grams/day for two and a quarter days!) was associated with a marked impairment of collagen-induced platelet aggregation. By constrast, aspirin ingestion did not inhibit ADP-induced aggregation. Sodium salicylate failed to prevent platelet aggregation either by collagen or ADP. Other groups\textsuperscript{22-24} confirmed and extended the original findings of Weiss and Aledort. The general conclusion was that aspirin – possibly by a poorly defined platelet membrane stabilizing effect\textsuperscript{25} – inhibited the platelet release reaction. The effects of aspirin ingestion occurred very rapidly but were of long duration (4 to 7 days), suggesting an irreversible damage to platelet population, which persisted until the affected platelets had been replaced by a sufficient number of new platelets. The critical role of the acetyl group in the aspirin effect was also rapidly singled out. Altogether, these findings reasonably explained the mild hemostatic defect produced by aspirin and indicated that it should be avoided in patients in whom control of hemostasis could be a problem.

«The Antichrist» – says William in The Name of the Rose – «can be born from piety itself, from excessive love of God or of the truth, as the heretic is born from the saint and the possessed from the sea».\textsuperscript{26} No surprise, therefore, that a more intriguing outcome of these studies was the possibility that, by inhibiting platelet aggregation, aspirin might be a useful anti-thrombotic agent. Platelet aggregates may form on collagen fibers which are exposed after the vascular intima has been broken. If aspirin was capable of inhibiting collagen-induced platelet aggregation, might it also prevent arterial thrombus formation? It was soon realized that this question could only be answered by clinical trials.\textsuperscript{27} In the early seventies, the opinion was prevalent that anticoagulant drugs – though effective in the management of venous thromboembolism – had not produced any significant effect on the overall morbidity and mortality from the complications of arter-
ial disease, such as myocardial infarction and stroke. Researchers such as the Canadian group of J.F. Mustard were reasoning that «assuming that thrombosis is involved in the death of patients with vascular disease who die from strokes or myocardial infarction, ..., the rationale behind the use of anticoagulant drugs in conditions where the initial accumulation of a platelet mass is the primary event in thrombus formation, is open to serious question». The case for testing aspirin in the prevention of myocardial infarction and other arterial occlusion disease became therefore very strong, although aspirin is a drug that any idiot can buy in any quantity he chooses and take for whatever condition he chooses. Strangely enough, aspirin was probably first tested in Europe as a prophylactic measure in post-operative venous thromboembolism. The results of this Medical Research Council of England’s trial were negative. We had to wait until the late eighties to be assured, by one of the largest and most complex meta-analyses performed in the past decade, that aspirin (and other antiplatelet drugs) were effective in the secondary prevention of different ischemic arterial diseases such as myocardial infarction and stroke and were possibly effective in the primary reduction of non-fatal vascular events in healthy subjects.

Development of platelet pharmacology

But let’s go back to the end of the sixties, when many different inhibitors of platelet function had already been described. In that period, two review articles were published which collated most of the information available on platelet inhibitors. Both articles made a distinction between inhibitors of ADP-induced aggregation and inhibitors of the platelet release reaction. Table 1 sets out the classification of anti-platelet compounds presented in these two review articles. On the basis of the evidence available in 1970, ADP appeared to be the principal mediator of platelet aggregation in physiological conditions. It is interesting to note that aspirin, diprydramole and sulfipyrazone, the first three drugs tested in large clinical trials for thrombosis prevention were identified as anti-platelet compounds between 1965 and 1968: they were all three already in clinical use for other indications and for many years no «new» antiplatelet compound came to the stage of clinical investigation. A few months after the publication of both review articles and of a book discussing the background for a clinical trial of aspirin in the prevention of stroke, a group of three articles in Nature New Biology reported that aspirin blocked the production of PGE2 and PGF2a in human platelets (and other experimental systems) and proposed – after more than 70 years of clinical use of this drug – that prostaglandin inhibition might explain some or even all pharmacologic properties and clinical effects of aspirin (and of all other non-steroidal anti-inflammatory drugs). The pharmacology of the anti-platelet drugs available in the late eighties (Table 2) with a historical review of the data and the concepts underlying their use was discussed in a chapter of a successful book. The interested reader will find there are several topics of some historical interest in the context of the present paper, the discovery of platelet and vascular arachidonic acid metabolism as a fashionable target for all anti-platelet drugs, the so called aspirin dilemma and its solution, the disappointment with the thromboxane A2-synthase inhibitors and sulfipyrazone, the liaison between diprydramole and adenosine, the development of ticlopidine as a mimic of Glanzmann’s thrombasthenia and many other intriguing observations. I shall recount here only some details of the aspirin dilemma.

Intermezzo: «The aspirin dilemma»

As already mentioned, on the basis of the knowledge available in the early seventies concerning the action of aspirin on platelets many clinical trials using aspirin as an antithrombotic agent in the secondary prevention of myocardial infarction and of cerebrovascular complications were initiated. However, very soon the discovery of PG12, a potent antiaggregating and vasodilating agent produced by vascular cells via the cyclo-oxygenase-initiated metabolism of arachidonic acid, cast serious doubt on the usefulness of aspirin as an antithrombotic drug. The simultaneous inhibition of TxA2 and PG12 synthesis could have been the reason for the disappointing results of early clinical trials on the antithrombotic effect of aspirin: failure of clinical trials still in progress was also anticipated. It was even shown that animals treated with high doses of aspirin, which inhibited PG12 synthesis, might have an increased thrombotic tendency. Moreover, humans taking high doses of aspirin exhibited a shortened bleeding time (Moncada, 1978). The assumption was made, and popularized, that to achieve antithrombotic efficacy, the inhibitory effect of aspirin on platelet cyclo-oxygenase should be retained, while that on the vascular enzyme should be minimized. Many clinicians were fascinated by this aspirin dilemma and urged pharmacologists to solve it rapidly. Several experimental approaches were therefore adopted to estimate the dose of aspirin which suppresses the synthesis of thromboxane A2, but not of prostacyclin. The initial approach was based on the assumption that the platelet enzyme would be more sensitive to aspirin than the vascular enzyme. Consequently, low dose aspirin was expected to achieve biochemical selectivity as only platelet cyclo-oxygenase would be affected. Although studies in vitro comparing platelets with cultured human endothelial cells, showed that aspirin exerted a similar inhibitory profile, the search for the lowest active dose of aspirin was intense; all attempts using single oral doses of aspirin failed to dissociate significantly the drug’s pharmacological effects on platelets and vascular cells, both in experimental animals and in man. Biochemical selectivity of aspirin was achieved for the first time in rats in a rather unusual way: an animal made thrombocytopenic by antiplatelet antibodies was exchange-transfused with blood from another animal pretreated with aspirin a few hours before (in order to allow complete elimination of
the intact drug from the peripheral circulation). The recipient rat had therefore aspirinated platelets but non-aspirinated vessel walls. Notwithstanding this pharmacologic success, the bleeding time of the animals did not change significantly. Biochemical selectivity was more easily demonstrated by administration of repeated small doses of aspirin. This was explained by the fact that platelet cyclo-oxygenase, once irreversibly acetylated by aspirin, could not be replaced as long as the affected platelets remained in circulation. As a consequence, the effects of single, partially effective doses of aspirin could be expected to accumulate – and this, in fact, occurred. However, the lack of effect of small dose aspirin treatment on vascular PGI2 generation was less uniformly accepted. For instance, cumulative inhibition of PGI2 synthesis measured on vascular segments was reported after repeated low doses of aspirin. One point of debate was that suppression of platelet TxA2 biosynthesis might not necessarily result in inhibition of platelet function in vivo. Evidence for an inhibitory effect of repeated low doses of aspirin on platelet function was provided by Wekslor et al. and De Caterina et al., studying platelet aggregation induced by single aggregating stimuli (agonists). However, when pairs of agonists (such as PAF and adrenaline) were used to induce platelet aggregation, repeated low doses of aspirin appeared to be no longer effective. The low-dose aspirin concept, though still debated at the experimental level, and before being evaluated in controlled clinical trials, received an enthusiastic reception from many clinicians. They were fascinated not only by the apparent simplicity of this pharmacologic approach, but welcomed the foreseeable reduction, or even disappearance, of side effects (mainly gastrointestinal) related to the chronic intake of relatively high doses of aspirin. This widespread attitude (at least in Italy) was soon supported by the results of six controlled clinical trials showing a dose-unrelated beneficial effect of aspirin in the secondary prevention of mortality in patients with myocardial infarction. The dose-unrelated beneficial effect of aspirin was confirmed in patients with unstable angina. To understand the clinical problem of the lack of dose-response relationship of aspirin better, some groups became interested in the possible effects of salicylate – this metabolite has a longer plasma halflife than the parent molecule and may accumulate during repeated drug administration. The importance of plasma salicylate levels in regulating the interaction

<table>
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<tr>
<th>Mustard and Packham</th>
<th>de Gaetano, Vermeylen and Verstraete</th>
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<td>I. Inhibitors of ADP-induced aggregation</td>
<td></td>
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<tr>
<td>a Inhibitors with structural similarities to ADP</td>
<td></td>
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<tr>
<td>b Inhibitors that bind calcium</td>
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<tr>
<td>c Inhibitors that affect the platelet membrane</td>
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<td>- Sulfhydryl group inhibitors</td>
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<td>- Fibrinogen degradation products</td>
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<td>d Factors influencing platelet metabolism or contractile protein</td>
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<td>e Miscellaneous (dextran, clofibrate,...)</td>
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| II. Inhibitors of platelet release reaction |
|   a Chelators of divalent cations |
|   b Metabolic inhibitors |
|   c Adenine compounds |
|   d Prostaglandin E1 |
|   e Colchicine |
|   f Methylenanthines |
| g Imipramine and amitriptyline |
| h Orthophosphonates |
| i Salicylaldehyde |
| j Adrenergic alpha-receptor antagonists |
| k Non-steroidal anti-inflammatory drugs and related compounds (salicylates,...) |
| l Phosphatidyl and sulfated polysaccharides |
| m Heparin and sulfated polysaccharides |
| n Glucosamine |
| o Dipyridamole and related compounds |
| p Fibrinogen degradation products |

| I. Inhibitors of the aggregating effect of ADP |
| 1. Synthetic inhibitors |
|   a Calcium-chelating agents |
|   b Arginine and guanidine derivatives |
|   c Sulfhydryl (dipyridamole and congeners, glycerylguaiacolate, nialamide,...) |

| 2. Biological inhibitors |
|   a Adenosine and analogous substances |
|   b Prostaglandins (PGE1, through adenylyl cyclase) |
|   c Fibrin(ogen) degradation products |

| II. Inhibitors of release of platelet ADP (inhibitors of' release reaction') |
| 1. Synthetic inhibitors |
|   a Acetylsalicylic acid and other anti-inflammatory agents (salicylates,...) |
|   b Antidepressant drugs |
|   c Miscellaneous (dextran, clofibrate,...) |

| 2. Biological inhibitors |
|   a Serotonin |
|   b Heparin |

| Factors influencing platelet function in vivo |
|   Evidence for an inhibitory effect of repeated low doses of aspirin on platelet function was provided by Wekslor et al. and De Caterina et al., studying platelet aggregation induced by single aggregating stimuli (agonists). However, when pairs of agonists (such as PAF and adrenaline) were used to induce platelet aggregation, repeated low doses of aspirin appeared to be no longer effective. The low-dose aspirin concept, though still debated at the experimental level, and before being evaluated in controlled clinical trials, received an enthusiastic reception from many clinicians. They were fascinated not only by the apparent simplicity of this pharmacologic approach, but welcomed the foreseeable reduction, or even disappearance, of side effects (mainly gastrointestinal) related to the chronic intake of relatively high doses of aspirin. This widespread attitude (at least in Italy) was soon supported by the results of six controlled clinical trials showing a dose-unrelated beneficial effect of aspirin in the secondary prevention of mortality in patients with myocardial infarction. The dose-unrelated beneficial effect of aspirin was confirmed in patients with unstable angina. To understand the clinical problem of the lack of dose-response relationship of aspirin better, some groups became interested in the possible effects of salicylate – this metabolite has a longer plasma half-life than the parent molecule and may accumulate during repeated drug administration. The importance of plasma salicylate levels in regulating the interaction
between aspirin and cyclo-oxygenase suggested that better knowledge of the pharmacokinetics of aspirin and salicylate might help resolve the aspirin dilemma. The pharmacokinetics of aspirin have been given little consideration in thrombosis prevention trials. The necessity to consider the pharmacokinetics of aspirin was strengthened by the observation that serum TxB2 generation was suppressed, even when there was no detectable aspirin in the peripheral blood in subjects taking oral aspirin.\(^{35-38}\) It was suggested that pre-systemic circulation first-pass deacetylation of aspirin was responsible for the low (or absent) peripheral drug levels (Figure 1). Thus, platelets passing through the gut capillaries could be acetylated by aspirin before reaching the systemic circulation, resulting in suppression of serum TxB2 generation, and the extent to which peripheral vascular cyclo-oxygenase might be affected could merely reflect the amount of intact aspirin which escaped first-pass metabolism (as well as hydrolysis by plasma esterases). The sparing of vascular cyclo-oxygenase after oral (compared with intravenous) administration of the same dose of aspirin was clearly shown in rats.\(^{39-40}\) It now appears that the concepts of low and high doses of aspirin, and of its biochemical selectivity in relation to platelet and vascular cyclo-oxygenase, are relative rather than absolute, and require to be qualified in relation to the drug’s pharmacokinetics. The aspirin dilemma was solved finally by determining the optimal conditions for pre-systemic acetylation of platelet cyclo-oxygenase in patients at risk for thrombosis. In young healthy subjects high-dose aspirin (650mg x 2) and indobufen (200mg x 2) – a cyclo-oxygenase inhibitor unrelated to salicylate – significantly inhibited serum TxB2 generation and the rise in tissue plasminogen activator actively induced by venous occlusion, without affecting the pre-occlusion values. In contrast, salicylate (569mg x 2, a dose equimolar to 650mg x 2 of aspirin) did not affect the fibrinolytic response. Moreover, low-dose aspirin (20mg x 7 days) while reducing serum TxB2 generation by about 90%, did not modify the increased fibrinolytic response to venous occlusion.\(^{41}\) The hypothesis that the rise in fibrinolytic activity occurring during this hypoxemic challenge is mediated by local generation of vascular PG\(_I_2\) was clearly demonstrated both in humans\(^{42}\) and in experimental animals.\(^{43}\)

Thus, any dose of aspirin which spares vascular cyclo-oxygenase activity would leave intact not only the anti-aggregating (i.e. PG\(_I_2\)) but also the fibrinolytic potential of the vessel wall. The aspirin dilemma could therefore have wider implications than simply the platelet-oriented TxA\(_2\)-PG\(_I_2\) balance.

**The Knights of the Round Table**

There may be moments in our life when we are either strongly convinced about something old or desperately looking for something new. In these very moments, either very near to or very far from us, something is happening that will dramatically change the rest of our lives. But quite rarely are we aware that the still unknown truth – within one hour or ten years – will not allow us to think in the same way again. In September 1970, a Round-the-Table Conference on Normal and Modified Platelet Aggregation was held in Leuven, Belgium.\(^{44}\) The intention was to assemble some European scientists who had contributed significantly to the rapidly developing field of platelet aggregation and
allow these workers to discuss a number of open questions. It may be of interest in this context to read the 15 questions asked by the Organizers (Table 3).

Among the 46 participants, almost all the historical contributors to platelet and hemostasis history in Europe were present, e.g. G.V.R. Born, K. Breddin, J. Caen, A.S. Douglas, R. Gross, R.M. Hardisty, H. Holmsen, J. Hugues, M.J. Larrieu, Y. Legrand, E.F. Lüscher, J.R. O’Brien, H. Poller, A. Sharp, J.J. Sixma, J.W. ten Cate, J. Vermeylen, and M. Verstraete. The Italians present were S. Coccheri, M.B. Donati, G. Leone, P.M. Mannucci, C. Praga and the author of this chapter. The structure of the meeting was rather unusual, as for each question prepared by the Organizers, there were two or three short introductory answers, followed by a lively and free discussion. Going now through these discussions may give the reader a unique flavor of what was the platelet and its role in hemostasis and thrombosis in Europe three decades ago. To the question «In which clinical conditions would pharmacologic inhibition of platelet aggregation be useful?», the answers were: cancer, hypertension, chronic glomerulonephritis, diabetes with thrombotic tendency, primary pulmonary hypertension... Summarizing recent data on Glanzmann’s thrombasthenia, J. Caen stated that this is «the most clearly defined disorder of hemostasis» yet «one does not know why the thrombasthenic palaelets do not aggregate in the presence of ADP». «We have» – concluded Caen – «many new findings on thrombsthenic platelets, but we do not know what is or are the underlying anomalies responsible for the absence of platelet aggregation in this disease». Four years later, Nurden and Caen65 made the seminal observations on platelet membrane glycoproteins which provided the basis for the tremendous development of our knowledge on hemostasis and thrombosis prevention.66,67

The other face of the moon
Possibly due to a continuous intellectual orientation towards America «buscando el oriente por el ponente», I was always attracted by the other face of the moon...

In 1977 an International Symposium68 was organized in Florence to discuss the platelet as a model of other cells and to evaluate its possible role in physiopathologic phenomena not directly related to hemostasis and thrombosis. Table 4 reports the titles of the six sessions of that Symposium. Now, many years after that Florence meeting, I am personally no longer directly engaged in platelet research, but younger people at the Mario Negri Sud research institute are actively involved in a new fascinating chapter of platelet function, namely the complex interaction of activated platelets with white cells (both polymorphonuclear and lympho-monocytes)

Table 3. Discussion to a panel of European experts of platelets in 1970.64

| Question N. 1 | A. Which hypothesis on platelet aggregation by ADP would seem to be most plausible?  
| Question N. 2 | B. Are cofactors of a protein nature involved in normal platelet aggregation?  
| Question N. 3 | What does the optical platelet aggregation test actually measure?  
| Question N. 4 | Which physical or chemical alterations of the platelet surface are provoked by different aggregating substances?  
| Question N. 5 | Role of the release reaction in platelet aggregation  
| Question N. 6 | How is platelet aggregation linked with increased availability of platelet factors 3 and 4?  
| Question N. 7 | Does rapid disaggregation following ADP-induced aggregation have any significance?  
| Question N. 8 | Are comparable results obtained with different “collagen” preparations?  
| Question N. 9 | Is aggregation by collagen and thrombin the consequence of ADP release only?  
| Question N. 10 | Do immunologic reactions provoke or modify the release reaction?  
| Question N. 11 | How does adenosine inhibit platelet aggregation?  
| Question N. 12 | Cyclic AMP, prostaglandins and platelet aggregation  
| Question N. 13 | Significance of congenital or acquired modifications of platelet aggregation  
| Question N. 14 | Inhibition of platelet aggregation by chemicals and drugs  
| Question N. 15 | In which clinical conditions would pharmacologic inhibition of platelet aggregation be useful?  
| Question N. 16 | Does an impaired release reaction really cause a haemorrhagic diathesis?  

Table 4. Platelets. A multidisciplinary approach.66

| Table of contents  
| I. Introduction  
| II. Platelets, endothelium, smooth muscle cells  
| III. Platelets and inflammation  
| IV. Platelets and immunologic reactions  
| V. Platelets and synaptosomes  
| VI. Platelets and tumor cells  

Figure 2. Hypothetical sequence of interactions between PMN leukocytes and activated platelets or injured endothelial cells. Reprinted from ref. 70, with permission.
and of activated leukocytes with platelets, the whole picture being taken - in flowing conditions - on the
background of endothelial cells. Whether the supposed new thrombogenic role of platelets summarized in
Figure 2 is of any clinical relevance will only be revealed in
another historical overview, some time from now.

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