PLATELET–VESSEL WALL INTERACTIONS

R. MICHAEL PITTILO
SAMUEL J. MACHIN (Eds.)

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With 55 Figures

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Cover illustration: Scanning electron micrograph showing discoid and activated platelets in contact with the arterial wall (×10 000).

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Series Editor's Foreword

The publication of *Platelet–Vessel Wall Interactions*, the second monograph in the Bloomsbury Series in Clinical Science, is particularly welcome as its appearance signifies the further development of the Series and its potential for the future.

The theme of this monograph is the pathophysiology of atherosclerosis, a topic that symbolises the aim of the Series, namely to highlight the important interfaces between basic medical science and clinical practice.

Our congratulations to the Editors and contributors.

London, December 1987

Jack Tinker

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Preface

In the Western world, atherosclerosis causes more illness and death than any other disease. Despite its devastating effects, the pathogenesis of the disease remains a matter for hypothesis and conjecture. This monograph owes its conception to a programme of work directed towards understanding the basic pathophysiology of atherosclerosis.

The circulatory system is lined by vascular endothelium which has a central role in maintaining the integrity of the vessel wall and preventing thrombosis. The natural equilibrium existing between normal endothelium which supports blood flow, and platelets which serve to repair damaged endothelium, is explored in the first two chapters.

Atherosclerosis developing as a response to endothelial injury is one hypothesis which has stimulated widespread interest, and research has largely been directed towards finding the injurious agent. There are many known risk factors for developing atherosclerosis—cigarette smoking, diabetes, hypertension and hyperlipidaemia—but a final common pathway of endothelial damage has not yet been defined. Using in vitro models, endothelium has been exposed to potentially toxic substances and circumstances, in an attempt to isolate the causal mechanism. The resulting effects on both structure and function of the vascular lining are discussed in detail.

In addition to basic pathophysiological research, our attention is also directed towards finding solutions to the clinical problems of established disease. The chapter on mesothelium outlines the experimental evidence for a novel solution to the problem of thrombogenic arterial prostheses.

Atherosclerosis is not the only disease to result from the malfunction of platelets and endothelium. Disruption of the equilibrium in the vessels of the kidney leads to life-threatening diseases, which are discussed in detail in Chapter 7.

The monograph ends with an account of new advances in the pharmaceutical field which may represent the mainstay of future treatment. Research will continue to discover and understand the fine

mechanisms controlling the normal vascular system and the problems that so commonly occur.

Acknowledgement

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May, 1986

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Contents

Chapter 1

The Platelet

Ian J. Mackie and Christopher R. Neal

Introduction

As long ago as 1882, Bizzozero recognised the important role that platelets play in thrombosis and haemostasis. Due to their complexity and reactivity, they are difficult cells to work with, and it is only recently that we have begun to understand their physiology and to realise that they are involved in a variety of cellular interactions and pathological states. In their normal non-activated state, platelets are small, anucleate discoid cells of 9.5 fl diameter; they are derived from megakaryocytes in the bone marrow, and normally circulate for 9–10 days at a count of $150–400 \times 10^9$/l (Burstein and Harker 1983). One third of platelets are normally stored in the spleen as an interchangeable pool with circulating cells, and can be pushed into the general circulation in times of stress. Platelet numbers are also increased in acute phase reactions and certain disease states, e.g. myeloproliferative diseases. They are very reactive cells, and on activation by suitable triggers, such as exposure to subendothelial tissues, they are able to adhere at the site of damage, release their contents, aggregate together and form a haemostatic plug. During these processes, platelets also assist fibrin formation by providing a surface on which many of the reactions of the coagulation "cascade" may occur. In a similar way, they later influence control mechanisms via protein C, antithrombin III and fibrinolysis. Many active substances are released: growth factors which influence smooth muscle cells in the vessel wall or tumour growth; serotonin, which affects vascular integrity; vasoactive materials which modulate local blood flow; and leucocyte chemoattractants. If these various functions go out of control, a pathological bleeding or thrombotic state may develop.

Morphology

Platelets display a complex internal morphology (Nichols et al. 1981; White 1983; White et al. 1981; Ulutin 1976). Four areas or zones are recognised on the basis of

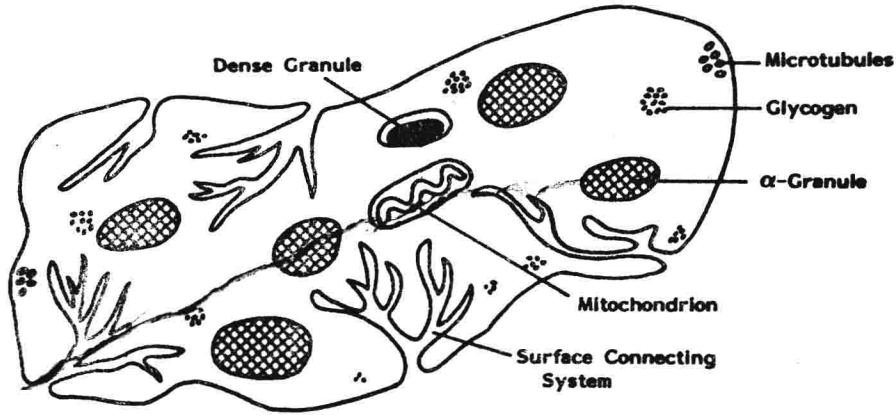


Fig. 1.1. Diagram of a typical non-activated platelet (in cross-section).

ultrastructural observations from scanning and transmission electron microscopy (SEM and TEM): the peripheral zone, the sol–gel zone, the organelle zone and the membrane systems (Figs. 1.1–1.5).

Peripheral Zone

This is composed of the limiting membrane and the submembrane filaments. The outer surface of the platelet is generally smooth with occasional indentations where openings of the surface connecting system (SCS) occur. The exterior coat or glycocalyx is thicker than on other cells and can be demonstrated by substances such as ruthenium red, colloidal iron or peroxidase conjugated antibodies. It is rich in glycoproteins, and contains receptors for prostanoids, coagulation factors, immunoglobulins, complement and other proteins. The membrane glycoproteins can be separated by SDS polyacrylamide gel electrophoresis (Ginsberg and Jaques 1983), and eight major bands (George et al. 1981) have been identified (Table 1.1). The platelet limiting membrane is similar in structure to the membranes of other cells, containing a variety of anion and cation pumps, e.g. Na/K ATPase, although freeze-fracture studies indicate that the platelet membrane possesses only small numbers of intercalated particles that are randomly dispersed. It is therefore likely that platelets have less transmembrane proteins than other cells. The membrane contains a phos-

Table 1.1. Platelet membrane glycoproteins: possible functions

Glycoprotein	Function
Ia	? Receptor for collagen
Ib	Receptor for thrombin and VWF
IIb IIIa	GIIb forms a calcium dependent complex with GPIIIa. This complex is a receptor for fibrinogen, VWF and possibly other adhesive proteins
V	Cleaved by thrombin; ? thrombin receptor
IX	Associated with GPIb; ? antigenic site for quinine/quinidine dependent antibodies

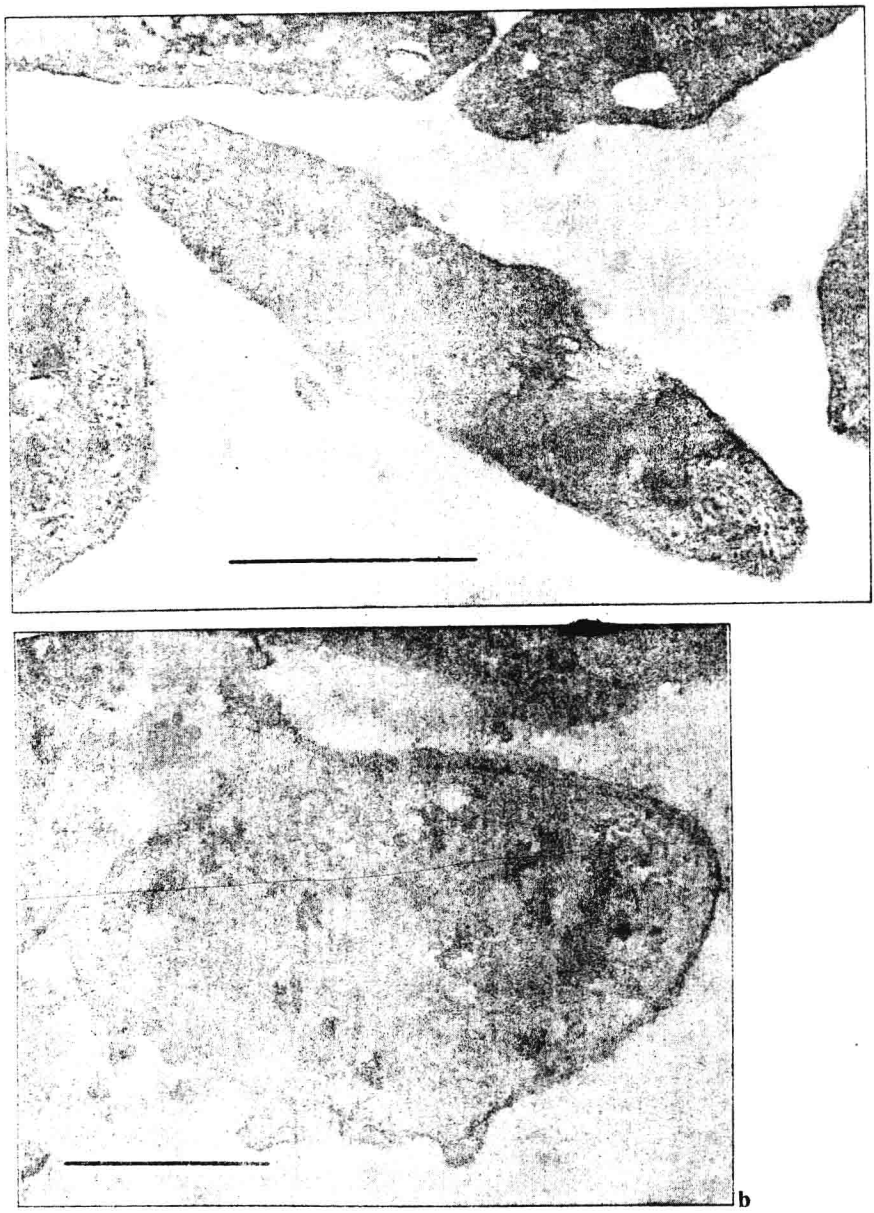
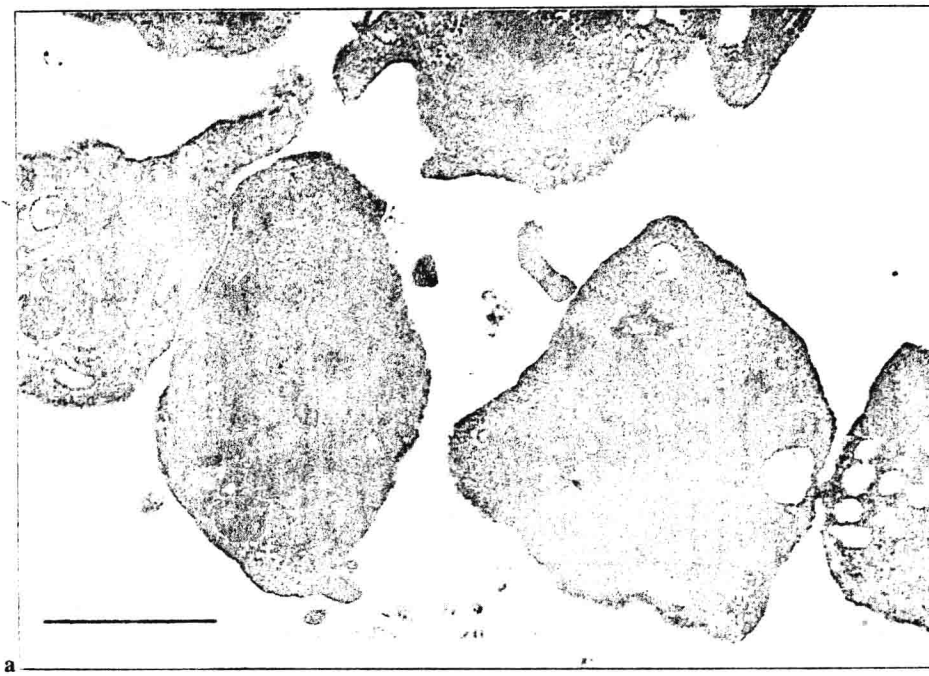
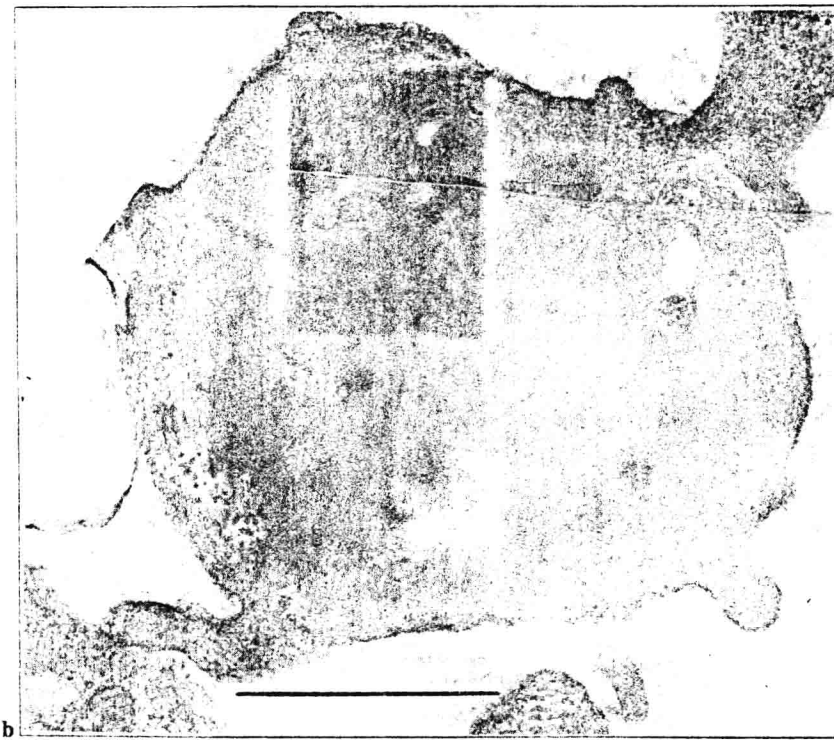


Fig. 1.2a, b. TEM of platelets. **a** Non-activated. **b** Minimal activation, pseudopods starting to form. Scale bars represent 1 μm.

pholipid bilayer with an asymmetrical distribution of phospholipids: phosphatidyl serine, phosphatidyl inositol and phosphatidyl ethanolamine are preferentially concentrated in the inner leaflet of the bilayer. The functional significance of this will be discussed in the section on Platelet Coagulant Activity.



a



b

Fig. 1.3a, b. TEM of platelets. **a** Activated, pseudopods present and interplatelet contact points developing. b Activated, pseudopods and some circumferential bands of microtubules. Scale bars represent 1 μm.

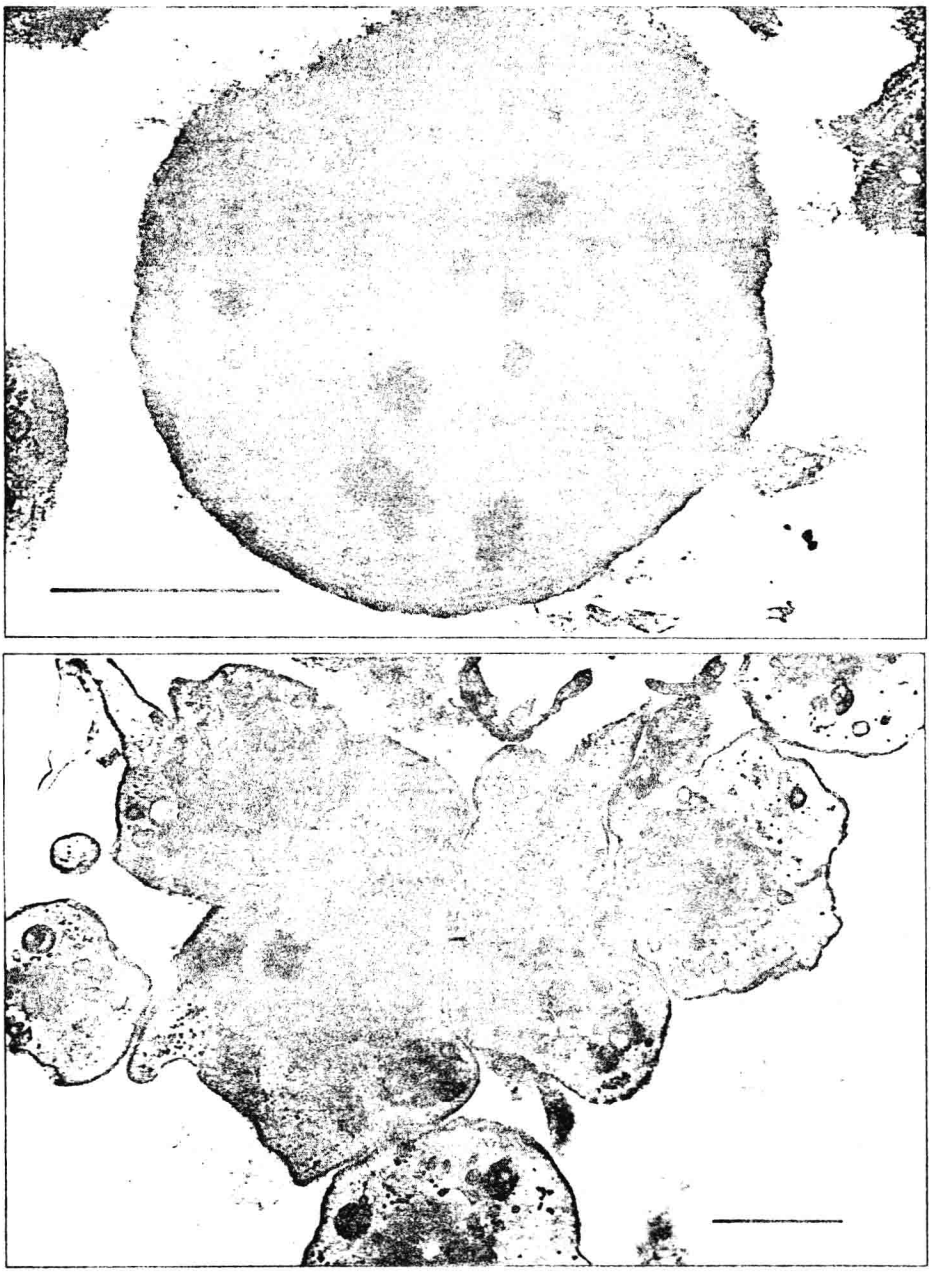


Fig. 1.4a, b. TEM of platelets. **a** Activated, granule centralisation with circumferential band of microtubules. **b** Aggregated platelets. Scale bars represent 1 μm.