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Manual of Blood Platelets Morphology, Physiology and Pharmacology



South Asian Society on Atherosclerosis and Thrombosis

Gundu HR Rao

Foreword
Jawed Fareed

JAYPEE

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CHAPTER 3

Platelet Morphology and Dysfunction

INTRODUCTION

Platelet production by the bone marrow megakaryocytes is regulated to maintain a constant functional platelet mass in the circulating blood. According to this line of thinking, platelet mass appears to correlate with functional ability than the platelet count alone, since several factors in addition to the platelet count have been shown to modulate the hemostatic function. On the other hand, in clinical situations where there is a need for platelet transfusion, in general, clinicians do not follow this line of approach. They keep transfusing platelet concentrates, till they approach an approved number of platelets in the blood.[1] Thrombopoietin helps maintain the number of circulating platelets by the bone marrow. The liver produces thrombopoietin at a constant rate like many other endogenous modulators and releases into circulation on demand. The circulating platelet count is close to 140,000–400,000/μL. Clinically relevant platelet disorders include abnormal increase in platelet number (thrombocythemia and reactive thrombocytosis), decrease in platelet count (thrombocytopenia), and platelet dysfunctions (hypo- or hyperfunction).

Acquired abnormalities of platelet function are very common and include drug interactions (heparin), pathogen interaction (dengue virus), systemic disorders, and interventional and surgical procedures.[2] Many disorders, such as myeloproliferative, myelodysplastic, uremia, macroglobulinemia, multiple myeloma, cirrhosis can impair platelet function. Hereditary intrinsic platelet disorders are rare and can cause lifelong bleeding tendencies. Diagnosis is confirmed by platelet function tests and ultrastructure studies. Since White and associates have done extensive studies of these rare disorders, we will describe some of them in the following paragraphs. Immune thrombocytopenia (ITP) develops from the interaction of an autoantibody that is directed at a structural platelet antigen. In children, viral antigens may trigger it. ITP worsens during pregnancy and is responsible for maternal morbidity and mortality. Platelet destruction and loss of function can develop as a result of variety of immunological causes (pathogen infections, drugs, connective tissue or lymphoproliferative disorders, and blood transfusions). Thrombocytopenic purpura (TTP), and hemolytic–uremic syndrome (HUS) are characterized by thrombocytopenia and microangiopathic hemolytic anemia.

GLANZMANN THROMBASTHENIA

Ultrastructural studies from various laboratories have demonstrated that membrane defects are common in abnormal cells from patients with inherited hemorrhagic platelet disorders. Thrombasthenia is a classical example of a defect in platelet–platelet interaction (cell–cell interaction). The inability

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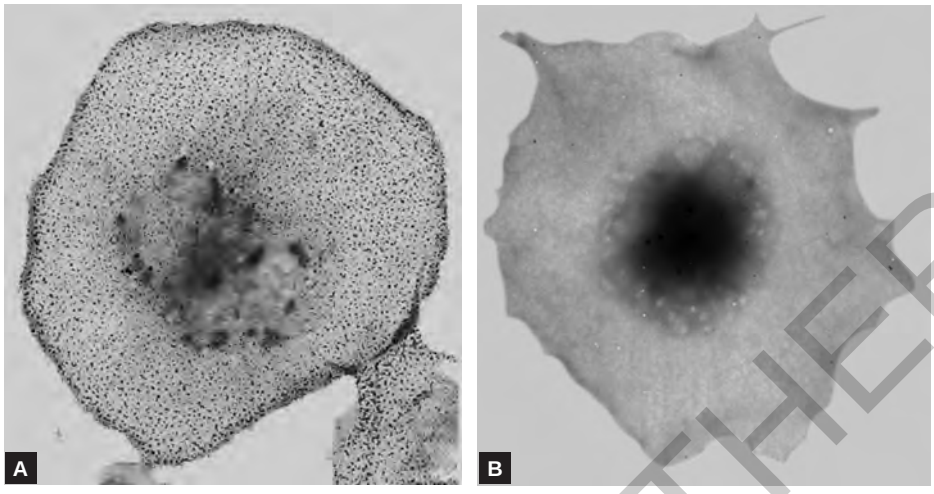

Figs. 3.1A and B: Platelets of Glanzmann thrombasthenia.

of patient's platelets to stick to one another is due to abnormalities of membrane glycoproteins (Figs. 3.1A and B). Glanzmann thrombasthenia (GT) is a rare genetic disorder, which manifests with hemorrhagic conditions. Under the guidance of Professor Mammen Chandy, Christian Medical College (CMC) Vellore, India had highlighted the frequency of GT in South India.[3] GT is a rare autosomal recessive disorder characterized by abnormalities in GPIIβ/IIIα (βII/αIII) receptor proteins. In this context, I would like to mention how bilateral collaboration was established between two great institutions. I was planning our Second International Conference on Thrombosis and Hemostasis at Bengaluru, Karnataka, India and I wanted to invite Dr Barry Coller, Clinical Professor, Mount Sinai School of Medicine, New York. USA. I knew his interest in GT studies and getting patients with this disorder was difficult in United States. I wrote to him that I could facilitate a working relationship with the CMC Vellore group, if he participates in our conference in Bengaluru. He graciously agreed and indeed participated in the SASAT-1996 conference in Bengaluru, which was organized under the leadership of Prof S. S. Iyengar.[4]

As a result of this initiative in 1995, a long-lasting relationship was established between Prof Mammen Chandy of CMC (Currently Director, Tata Memorial Cancer Center, Kolkata) and Prof Barry Coller of New York (Currently at The Rockefeller University, USA). The two groups together were able to work on the molecular diversity of GT in southern India.[5,6] They were able to identify 10 "novel" mutations from 16 unrelated patients, demonstrating the genetic diversity of the disorder in southern India.[5] As an extension of this study, they conducted mRNA splicing and highlighted the role of specific amino acids in structure–function correlations of αIIb/β_3.[6] Both groups have published their work on prenatal diagnosis of this disease.[7,8] Dr Coller and his staff have continued their studies on the genetic and protein abnormalities responsible for the disease, as well as variants in the genes for the receptor (*ITGA2B* and *ITGB3*). Looking back at the three decades of research progress on this work, it makes me feel happy to note that

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it has resulted in screening of the *ITGA2B* and *ITGB3* genes in large international cohorts.[9] In this study, researchers were able to sequence the coding of the regions and splice both the genes of 76 affected families and identified 78 genetic variants (55 novel) suspected to cause GT. These seminal studies extend our knowledge of GT and the pathophysiology of an integrin to molecular level.

A variety of molecules are stored within the α and dense granules of the platelet, which upon activation of the platelet, are released into the external environment of the platelet. The storage pool disorders are a result of the deficiency and/or abnormality of either or both types of granules. In these disorders, secretion is hindered, not by the secretory mechanisms, but by the lack of content within the granules. Both granules appear to develop from the homotypic fusion of trans-Golgi vesicles in megakaryocytes as well as from heterotypic fusion of these vesicles with endocytic vesicles from the plasma and plasma membranes.

According to White, the primary congenital release disorders are a heterogeneous group of disorders with a wide variety of underlying defects whose mechanisms are not yet fully elucidated. They can be caused by abnormalities of signal transduction from the membrane (receptor or G-protein defects or mutations), abnormal internal metabolic pathways (mutations or defects of enzymes, i.e. PLC, PKC), abnormal release mechanisms, abnormal structures involved in the release reactions. The common abnormality within this group of defects is the failure to successfully release granule contents upon platelet activation. Release defects are associated with prolonged bleeding time, abnormal in vitro platelet aggregation profile in association with ADP (including an absent secondary wave) and epinephrine and collagen with a blunted or absent secondary wave.

Abnormalities of platelet secretion can be due to deficiency of platelet granules or defects in the signal transduction events that regulate secretion or aggregation. Platelet storage pool disorders can be congenital or acquired and result from a deficiency of granules (α or dense granules, or both) or a defective release of granules at platelet activation. Dense granule storage pool disorders (δ-SPDs) can appear as a singular clinical entity or as part of other hereditary disorders, such as Chediak–Higashi, Hermansky–Pudlak, or Wiskott–Aldrich syndrome (WAS). [14]δ-SPD often shows decreased aggregation response to ADP, epinephrine, and collagen and normal aggregation to arachidonic acid and ristocetin. Ultrastructural abnormalities in these disorders usually show decreased dense granules. Furthermore, α-SPD [gray platelet syndrome (GPS)] has decreased α granules and is usually considered a macrothrombocytopenia. White has described ultrastructural pathology of a variety of rare platelet disorders.[10-39] Additional references can be accessed at the following link at www.labome.org., under James G White, University of Minnesota.
(https://www.labome.org/expert/usa/university/white/james-g-white-452177.html).

COMMON PLATELET DISORDERS, BIOCHEMICAL AND CLINICAL FINDINGS

Storage Pool Deficiency

Storage pool deficiencies are a group of disorders caused by problems with platelet granules, which are little sacks containing various proteins, enzymes, and other constituents. There are two types of granules recognized:

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α granules and dense granules (dense bodies). Storage pool deficiencies are caused by a lack of granules; by and large, most common ones are caused by a failure of the platelets to empty or release the contents of the granules. Release defects are a diverse group of disorders caused by a problem with the secretory mechanisms. Even though the granules are present within the platelets, their contents are not released upon activation to the circulating blood. Delta storage pool deficiency is caused by a lack of dense granules and the components normally stored within them. This type of bleeding problem can be a feature of other inherited conditions such as Hermansky-Pudlak, Wiskott-Aldrich, and Chediak-Higashi syndrome (CHS). The four major types of congenital platelet storage pool disease identified are dense body deficiency (decreased dense bodies with serotonin and ADP), gray platelet syndrome (decreased α granules and contents), factor V Quebec (protease degradation of α granules), and mixed α-granule/dense body deficiency (decreased α-granules and dense bodies). In δ-SPD, the δ granules (dense bodies) are affected, and in α-SPD, it is the α granules (Table 3.1).

Hermansky–Pudlak Syndrome

Hermansky–Pudlak syndrome (HPS) is a disorder characterized by oculocutaneous albinism, which causes abnormally light coloring of the skin, hair, and eyes. Nine different types

Table 3.1: Platelet disorders, biochemistry and clinical findings.

Platelet disorders	*Biochemistry*	*Clinical findings*
von Willebrand (vWF) (defect in adhesion)	Decreased vWF on platelet membrane	Bleeding mild to severe
Bernard-Soulier (defect in adhesion)	Lacks GpIb/IX, unable to adhere to platelets	Severe bleeding tendencies
Glanzmann thrombasthenia (defect in aggregation)	Lacks GpIIb/IIIa, unable to bind fibrinogen	Varied bleeding possible mucous membranes
Storage pool disease (defect in secretion/release)	Dense granule deficiency, no release	Varied bleeding mild to severe
Hermansky–Pudlak (defect in secretion/release)	Lipid metabolism disorder that causes deficient release of platelet granules	Albinism, mild bleeding
Wiskott–Aldrich (defect in secretion/release)	Structurally abnormal platelets	Severe eczema infections
Chediak–Higashi (defect in secretion/release)	Lack dense bodies and ADP	Albinism, infections hemorrhage
Gray platelet syndrome (defect in secretion/release)	Deficiency of platelet α granules	Mild bleeding
Scott syndrome (defect in coagulation support)	Abnormalities of the platelet surface membrane that fail to promote activation of the blood clotting proteins, which are necessary in the formation of the fibrin clot	

Source: Huebsch LB, Harker LA. Disorders of platelet function. West J Med. 1981;134(2):109-27.

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of HPS have been identified (https://ghr.nlm.nih.gov/condition/hermansky-pudlak-syndrome). Several types of HPS have been described in patients from Puerto Rico.[40] Mutations in one of the nine genes (*HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DYNBP1*, *BLOC1S3*, and *PLDN*) are responsible for this disorder. The HPS is a mild bleeding disorder in which the platelets are markedly deficient in the storage pool of adenine nucleotides and serotonin. These products are normal, stored in a specific type of storage organelle, the dense body. HPS platelets appear unable to form these organelles or cannot concentrate the products in them due to an organelle membrane abnormality. Witkop and White shared NIH grants for several years to conduct studies on this rare disorder.[39-44] Majority of patients were from Puerto Rico.

Basically, this is an autosomal recessive disorder causing oculocutaneous albinism and a platelet storage pool deficiency, reflecting defective biosynthesis and/or processing of melanosomes and platelet dense bodies (Figs. 3.2 and 3.3). Four human genes (*HPS1*, *ADTB3A*, *HPS3*, *HPS4*) are associated with four subtypes of HPS. The most common is *HPS1* in which a 16-bp duplication in exon 15 of the HPS gene seems to be the cause of 450 non–Puerto Rican patients.[44-46] Witkop and White studied HPS patients from different parts of the world. I remember fondly the days that I used to visit various hospitals in India to collect hair and platelet samples for their studies. For additional references to their collective work, search Witkop CJ and White JG.

Wiskott–Aldrich Syndrome

Wiskott–Aldrich syndrome (WAS) is characterized by abnormal immune system function and a reduced ability to form blood clots. This condition primarily affects males. Individuals with WAS have microthrombocytopenia, which is a decrease in the number and size of blood cells involved in clotting (platelets). This platelet defect, which is present from birth, can lead to easy bruising or episodes of prolonged bleeding. This syndrome is a rare X-linked primary immunodeficiency condition characterized by repeated infections, hematopoietic malignancies, eczema, and thrombocytopenia. Studies have demonstrated both signaling and cytoskeletal abnormalities in lymphocytes of WAS.[47] The gene responsible for WAS, a disease affecting platelets and lymphocytes, has been cloned and its protein product has been

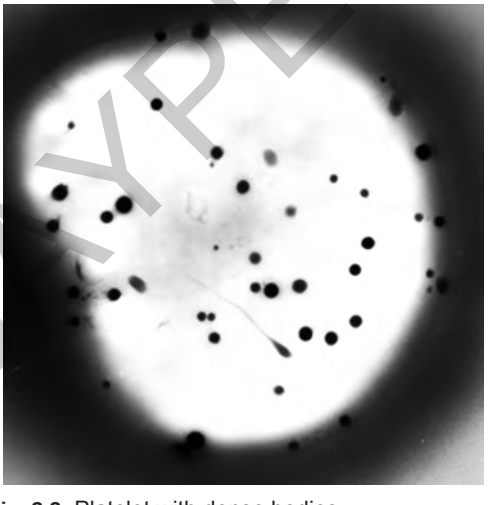

Fig. 3.2: Platelet with dense bodies.

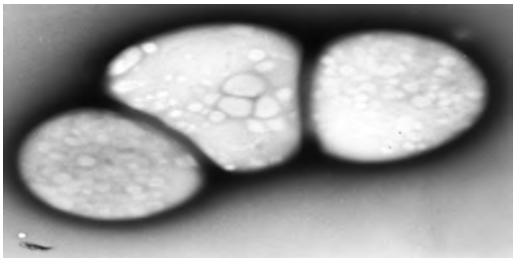

Fig. 3.3: Hermansky–Pudlak syndrome—platelets with no dense bodies.

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found to interact with the GTPase Cdo42. WAS protein (WASP) seems to provide a link between Cdc42 and the actin cytoskeleton.[48] This is a complex primary immunodeficiency disorder and its gene product WASP is a key regulator of actin polymerization. Severe manifestation of WAS leads to an early death from infection and bleeding. Currently the only therapy seems to be allogeneic stem cell gene therapy.[49] After successful therapy, the authors concluded that hematopoietic stem cell gene transfer may achieve complete immunological correction without producing the toxic effects implicit in the concept of retrovirus-based stem cell gene transfer.

Chediak–Higashi Syndrome

Giant cytoplasmic granules are the hallmark of the patients with CHS. In addition to the high frequency of giant granules, platelets from most patients with this disorder are deficient in the storage pool of adenine nucleotides and serotonin and the dense bodies in which they are sequestered (Fig. 3.4). CHS is a rare autosomal recessive congenital

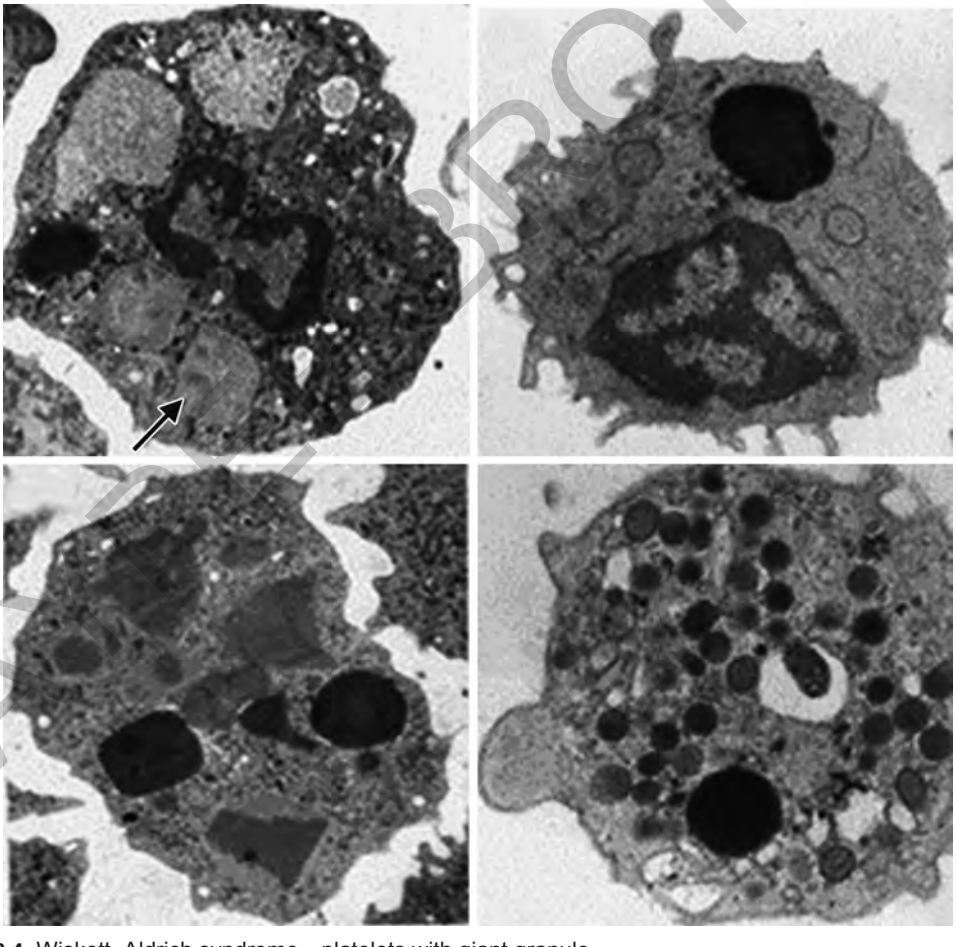

Fig. 3.4: Wiskott–Aldrich syndrome—platelets with giant granule.

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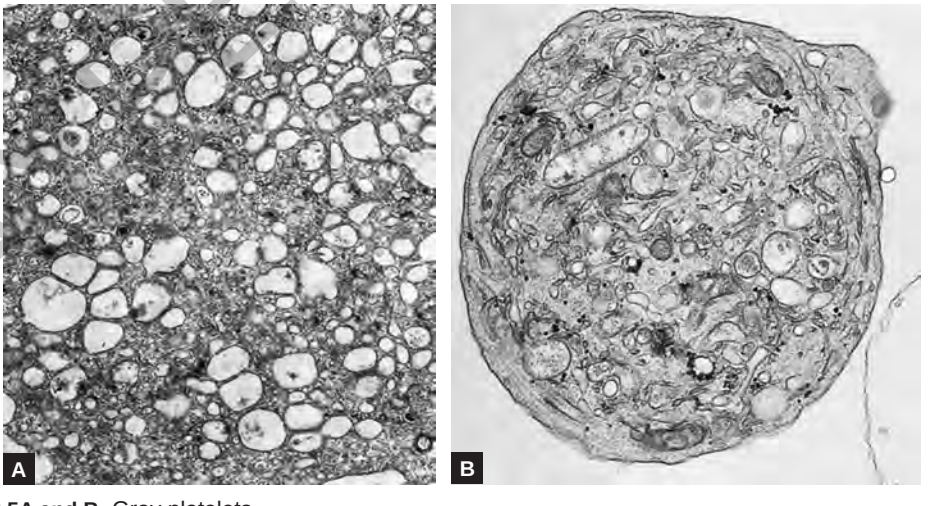
immunodeficiency caused my mutations in *CHS1*, a gene encoding a putative lysosomal trafficking protein. Platelets from patients presenting with childhood CHS have been reported to be deficient in dense bodies.[50,51]

Gray Platelet Syndrome

The GPS is another example of an organelle membrane defect. Gray platelets develop normal numbers of dense bodies and lysosomes, but appear selectively unable to form the membranes necessary to enclose α granules. According to White, "by elimination, the only morphologically distinguishable organelle in which gray platelets could be defective is the granule secreting B thromboglobulin, fibrinogen, thrombin-sensitive protein, platelet factor 4 and mitogenic factors". He also explored the possibilities that the large number of vacuoles (Figs. 3.5A and B) seen in gray platelets were meant as storage sites for missing products. Since ultrastructural studies revealed that these platelets have α granules less than 15% of normal, further biochemical studies were initiated to characterize the defects.[52] Platelets from both patients had severe deficiencies of platelet factor 4 and β thromboglobulin. They were also deficient in thrombin-sensitive protein, as well as platelet-derived growth factor.

von Willebrand Factor Disease

The defect in von Willebrand factor (vWF) resides within the vWF, which plays an important role in platelet function. Interactive platelet receptor for this protein is GPIb/IX. Abnormalities of vWF may lead to mucocutaneous bleeding similar to that seen in other platelet function defects. This is inherited as autosomal dominant trait with males and females are equally affected.[53] This disease is classified to three types: type 1 includes partial quantitative deficiency, type 2 includes qualitative defects, and type 3 includes virtually complete deficiency of vWF. According De Jong et al. once the vWF is confirmed by functional tests, subtyping tests can classify the patients as von Willebrand disease (vWD) 1, 2, or 3. The performance of some additional



Figs. 3.5A and B: Gray platelets.

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assays and analyses, such as vWF propeptide measurements or genetic analyses may help identifying the pathological mechanism behind certain defects or can guide in the choice of treatment.[54]

Bernard–Soulier Syndrome

The abnormal platelets of patients with Bernard–Soulier syndrome (BSS) are capable of adhering to one another, but fail to stick to the site of vessel wall injury. Defective platelet function in this disorder appears related to a marked deficiency or absence of a surface membrane glycoprotein different from the glycoprotein abnormalities of GT. Decreased or absent expression of the GPIb/IX/V receptor due to mutations in the *GP1BA*, *GP1BB*, or *GP9* genes gives rise to BSS (Fig. 3.6).[55]

BSS is characterized by the inability of the platelets to bind to vWF during the initial steps of platelet adhesion because the platelets either lack or have qualitative defect in the platelet membrane glycoprotein GPIb–IX–V complex. Mutations leading to absent expressions or dysfunctions have been uncovered in the gens for GPIbα (CD42b) and GPIX (CD42a). Mutations in GPIbα can lead to platelet-type vWD in which GPIb–1X are expressed normally but bind vWF spontaneously, which leads to platelet aggregation and thrombocytopenia. BSS is nearly always inherited in an autosomal recessive manner, with consanguinity a frequent finding. Just a few representative rare platelet function disorders have been presented in this section. Readers are urged to refer to comprehensive reviews on the molecular basis of these disorders as well as management of such bleeding disorders under clinical conditions.[56-65]

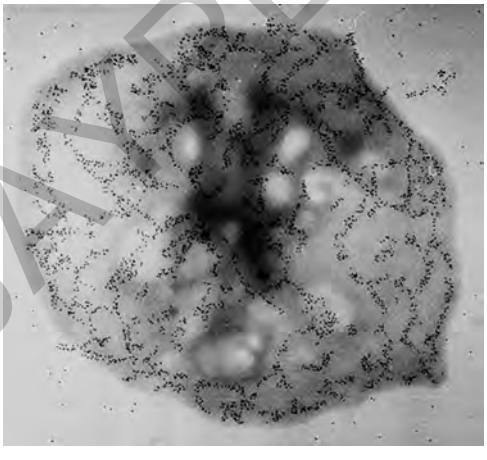

Fig. 3.6: Platelet of BSS patient.

MISCELLANEOUS DYSFUNCTION OF PLATELET FUNCTION

Cyclooxygenase Deficiency

Studies from our laboratory at the University of Minnesota did not reveal "aspirin resistance" in any individuals tested. All the subjects tested responded with aggregation when stimulated with arachidonic acid (AA). However, evaluation of physiology, biochemistry, ultrastructure, and function in a young woman without history of any hemorrhagic problems revealed that her platelets were deficient in cyclooxygenase (COX) activity. Her platelets aggregated in response to thrombin, ADP, and collagen but failed to respond to AA even at as high a concentration as 2 mM. Amounts of ^{14}C-AA released after stirring with thrombin were similar to normal platelets. However, evaluation of prostaglandin synthesis after stirring with radiolabeled AA revealed no evidence of endoperoxides or thromboxane synthesis, although products of lipoxygenase were produced in normal amounts. Preexposure to 5 uM epinephrine, a concentration that gave only a primary wave response to AA resulted in normalization of her platelet response

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to AA. These observations may explain why patients with platelet COX deficiency have mild absent bleeding symptoms.[66] In a separate study, we demonstrated that a mechanism of membrane modulation, mediated by α-adrenergic receptors cooperatively linked to the endoperoxide and thromboxane receptor can secure irreversible aggregation response in normal and abnormal platelets despite absence of secretion (ADP) and prostaglandin synthesis.

Endoperoxide/Thromboxane Receptor Dysfunction

Extending these studies, we were able to demonstrate existence of such dysfunctions in dog platelets and the ability of the mechanism of membrane modulation to restore the function in these defective platelets.[67,68] Dogs have platelets, which are heterogeneous in regard to their aggregation response to arachidonate. Since prostaglandin metabolism is intact in these platelets, the observed dysfunction appears to be the result of variable sensitivity to endoperoxide and thromboxane A_2. Preincubation of platelet-rich plasma (PRP) with epinephrine uniformly transforms PRP, which does not aggregate with upon exposure to arachidonate alone into arachidonate responsive.[67] Johnson and associates demonstrated that in most of dogs, mongrel or purpose bred, have platelets that generate TXA_2 but fail to aggregate irreversibly or secrete granule contents.[68] These TXA-insensitive platelets do not respond to TXA analogs, U46610, or I-BOP. However, 30% of the mongrel have normal platelets that respond to PG-endoperoxides and TXA. Similar to what we found with COX-deficient human platelets, this genetically inherited receptor abnormality in dogs do not cause any bleeding diathesis. Johnson and associates have done extensive studies on the biology of TXA receptor in platelets as well as the Gx_q and Gx_{11} gene expression in platelets.[68-70]

Platelet Dysfunction in Animal Platelets

Animals are used as experimental models in a variety of studies. In addition, millions of animals are used as domesticated pets. Therefore, it is important to understand the subtle difference in the mechanisms involved in hemostasis and thrombosis. From the point of view of medical device developer for instance, preferred route has been to develop their device in animal models, which are relatively nonresponsive for thrombotic episodes. As an example, much of the work on heart valves, stents, and artificial heart is done using animals, such as goats, cows, or horses. Platelets of these animals are less responsive to the activation stimulus than human platelets. Of course from the point of consumers, this is not the best approach. These tests have to be done in animals that have platelets, which are functionally similar to human platelets (porcine or primates). I have had discussions about this dilemma with funding agencies as well as device development companies. In view of the fact that it is convenient to work with these established animal models, which are less risky, the device companies prefer to use these animal models (goats, sheep, cows, or horses). The funding companies also do not want to take any risk and spend additional funds to develop newer better reliable animal models.

White and associates studied ultrastructure, physiology, and function of blood platelets in a variety of animals, including, dogs, cows, horses, sheep, goat, turkeys, camels, elephants, and Beluga whales. We have already described in the preceding paragraphs about

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our findings on dog platelets. In the following paragraphs, we will describe briefly about our work on platelet function in other animals. Before I get into the details of platelet dysfunction in animals, I would like to mention, for various reasons, each group preferred to work with blood platelets from a different species. For instance, VA medical Center at Minneapolis, Minnesota, researchers preferred to work with dog platelets. At the Mayo Clinic, Rochester, MN, Dr Bowies' group worked with a "vWF model" with pigs. Canadian researchers at McMaster's University studied rabbit platelets. Chocolate City, Hershey Pennsylvania, used cow platelets for their studies. Utah Heart Institute used horse platelets for their studies. This preference was partly due to the availability and partly due to their earlier experience and publication records.

Bovine Platelets

Human platelets react to surface activation by losing their shape, extending pseudopods, converting to dendritic forms, and finally spreading. Bovine platelets do not spread, rather they unfold (Fig 3.7).[71] Surface activation causes them to transform from disks to irregular flattened shapes resembling dendritic platelets. Bovine platelets lack surface-connected open canalicular system (OCS), which serves as a reservoir of membranes for human platelet spreading.[72]

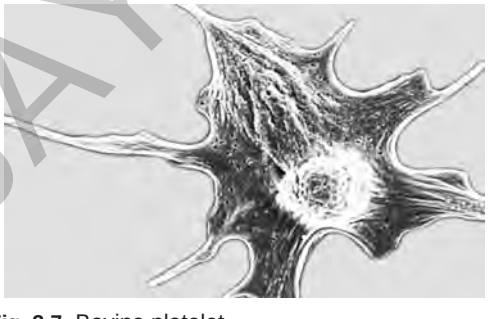

Fig. 3.7: Bovine platelet.

Furthermore, the microtubule coils are more resistant to disassembly in surface-activated bovine platelets. Fibrinogen-gold particles are moved to the interior of human platelets rapidly; bovine platelet receptors hardly internalize F-gold. Human platelets aggregate when mixed with bovine plasma, but bovine platelets do not respond to human plasma. Bovine platelets in citrate buffer poorly react to the subendothelium, whereas suspended in heparinized blood reacted and adhered more readily than human platelets. There seems to be different mechanisms involved in hemostasis in human and bovine species.

Horse Platelets

Collaborating studies were done with the veterinary laboratory at the University of Minnesota on platelet function disorders in racing horses. Platelet function was evaluated in horses with exercise-induced hemorrhage (bleeder) and in control horses (nonbleeder). Platelet aggregation, secretion, and adhesion to rabbit aortic subendothelium were similar for bleeders and nonbleeders. University of Kentucky has maintained a record of all the publications on this topic from 1990 to 2005. See link (http://www2.ca.uky.edu/gluck/images/info%20pages/BibEIPH.pdf). Exercise-induced pulmonary hemorrhage (EPIH) is seen in most race horses and in many other horses used in equine sports. Blood in the tracheobronchial tree is identified in 4–75% of racehorses via endoscopic examination, and hemorrhage is detected by cytological examination of bronchoalveolar lavage in more than 90% of racehorses. Weiss et al. at the University of Minnesota evaluated the platelet function of both bleeder and nonbleeder horses. Platelets readily aggregated

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in response to ADP, thrombin, collagen, and arachidonic acid. On the basis of their results, they concluded that horses might be predisposed to thrombus formation and subsequent microvascular obstruction.[73] One may also speculate couple of scenarios to explain this phenomenon. When we were trying to do studies on dog platelets, we found that when they are excited, due to the adrenalin rush, platelets would disappear from the circulation (sequestered). However, when the dogs are calm and conditioned to the blood-drawing procedure, we could find normal platelet counts. This fits with the experience of racehorse managers, who observed prior conditioning of thoroughbreds for short periods reduced the incidence of bleeding during the races. On the other hand, adrenaline rush induced by the racing event could produce a thrombotic state in the thoroughbreds, as speculated by Weiss and associates and cause microvascular obstruction. There is a great need for further studies to determine the underlying cause for exercise-induced (adrenalin-induced?) pulmonary hemorrhage.

Turkey Platelets

Turkeys are hypertensive birds compared to mammals of similar size. We studied in vitro synthesis of thrombocyte TXA, 12L-hydorxy-5, 8, 10 heptadecatrienoic acid (HHT), 12L-hydorxy-5, 8, 10, 14 eicosatetraenoic acid (HETE), and aortic prostaglandins (PGs) in 1–10-month-old domestic white turkeys.[74] TXA production was increased and HETE production was markedly reduced in normal thrombocytes. These studies also demonstrated that there was considerable deficiency in PGI_2 production. The vasopressor effect of PGE_1, PGE_2, and PGI_2 was altered in awake turkeys. Both vascular AA metabolism and vasodepressor potencies of PGE_1 and PGI_2 were altered and the activity of lipoxygenase pathway in thrombocytes was limited.

Acquired Platelet Disorders

Several diseases, procedures, and drugs have been associated with acquired platelet function disorders.[2,62,75,76] Hyperglobulinemia associated with multiple myeloma induces a platelet membrane defect resulting in impaired hemostatic function. In uremia associated with any form of renal disease, platelet adhesion and aggregation are decreased. Similarly, chemotherapy may also cause platelet dysfunction. Pathogens, such as dengue virus are known to cause severe loss of circulating platelets.

Numerous drugs can impair platelet function. Drugs reported to block platelet receptor binding or to change platelet membrane charge or permeability include furosemide, penicillin, carbenicillin, lidocaine, phentolamine, and chlorpromazine. Drugs that inhibit transduction of messages received at the platelet surface include caffeine, theophylline, dipyridamole, and papaverine. Drugs that inhibit execution of platelet responses (aggregation, secretion, or thromboxane production) include aspirin, indomethacin, acetaminophen, phenylbutazone, ticlopidine, pentobarbital, and sulfinpyrazone. Heparin-induced thrombocytopenia is well recognized by the clinical community.

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Manual of Blood Platelets
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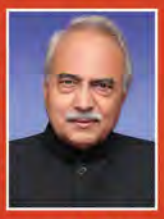
This is the best one among all monographs on Platelets, put together by Professor Gundu HR Rao. There is the description of the roles of the cells in hemostasis and thrombosis at an extended level. Platelet story has been narrated with beautiful electron photomicrographs and original illustrations. This monograph includes discussions on aspirin resistance, unique mechanism of platelet membrane modulation, platelet interactions with vascular surfaces, biomaterials, and biomedical devices, etc. Furthermore, the book includes over 1000 references related to our work at the University of Minnesota (1970–2015). The monograph provides a comprehensive overview of the work done at the Thrombosis Research Laboratory, Lillehei Heart Institute, University of Minnesota, USA for over four decades by Professor (Late) James G White and Dr Gundu HR Rao.

The monograph includes chapters on ultrastructure morphology, platelet dysfunction, platelet physiology, platelet activation mechanisms, role of calcium in platelet activation, role of eicosanoids, cAMP and cGMP, antiplatelet drugs, antiplatelet therapies, aspirin resistance, platelet dysfunction in diabetes, platelet membrane modulation, platelet vessel-wall interactions, and blood biocompatibility. Authors hope that this collective work on Platelet Physiology and Pharmacology will serve the students, clinicians, and researchers as a useful reference monograph.



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