GENESIS AND COMPARISON OF MAMMALIAN BLOOD PLATELETS

by

THOMAS EDWARD NIGHTINGALE

A. B., Kansas State University, 1964

A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Zoology

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1966

Approved by:

Major Professor

Table of Contents

HISTORY

The mammalian blood platelet was first described by A. Donne in 1842, when he stated that "there exist in the blood, red and white globules and little globules or 'globulins' (Tocantins 1948). Zimmerman, in 1846, believed "elementarblaschen" were precursors of red blood corpuscles, though he remarked on their tendency to gather in clumps (Tocantins 1948). The platelet was alternately described as a product of leukocyte destruction, bacteria, granular masses, or precursors of red blood corpuscles (Osler 1905; Tocantins 1948), until Bizzozero in 1882 observed the circulation of platelets in living animals (Tocantins 1948). This work by Bizzozero was corroborated by Howell in 1884 (Tocantins 1948).

At a medical meeting in Baltimore, a report was presented by a Professor Kemp who found that defibrinated blood refused to clot, and the platelets disappeared (Osler 1905). At the same meeting, it was reported by a Doctor Bogge that platelets and coagulation were associated since the addition of pure platelets to fibrinogen produced rapid coagulation, while the addition of leukocytes brought about a very slow coagulation (Osler 1905).

Wright (1910) carried out an extensive program which proved the derivation of platelets from megakaryocytes in several mammals. Duke (1910) associated platelets with hemorrhagic disease and described two criteria, (the bleeding and coagulation time), for determining the severity of the diseases.

COMPARATIVE ASPECTS

Comparative studies of platelets and their premammalian homologue, the thrombocyte, are relatively scarce in the literature. This dearth is not due to a lack of knowledge of their existence, since Bedson (1923) stated his belief that mammalian platelets and avian thrombocytes were homologous, although the nuclei of the platelets were supposedly lost prior to maturation, just as with the red corpuscles. Wright (1910) reported that megakaryocytes were found only in mammals, but made no reference to corresponding cells in premammals. Jordan (1933) noted spindle cells in certain polychaetes and cyclostomes which he considered to be lymphocytes. In this same study Jordan found similar fusiform lymphocytes in the blood of hagfish and lampreys, but made no mention of platelets or thrombocytes.

Forkner (1929) characterized thrombocytes as about the size of a lymphocyte, irregular in shape, and possessing a nucleus which often appears vacuolated. He commented on their tendency to clump in a manner similar to mammalian platelets. This paper stood alone until 1962 when Shirakawa undertook a survey of the coagulation mechanisms of fish, turtles, alligators, skates, sharks, birds and humans. This investigator utilized morphology, staining characteristics (for glycogen content), and thrombocyte behavior during clotting to show the similarities in the coagulation process.

Until the late 1950's, many of the reports concerned with comparative studies of the hematologic make-ups of various animals dealt only with the erythrocytes and leukocytes. Some investigators described platelet morphology, a few made platelet counts, but most simply ignored the platelets. Among the workers who performed platelet counts, Mayerson (1930) found

621,000 per cu. mm. for the dog; Lawrence (1947) gave 422,000 per cu. mm. as the average number found in cats; Casey (1936) reported 583,000 per cu. mm. for adult male rabbits; and Salvidio (1960) reported 416,000 per cu. mm. for a colony of mixed rabbit breeds. Two groups of workers investigated sex differences in platelet counts and arrived at an impasse. Cameron (1949) found that male albino rats had higher platelet counts than females (673,000 per cu. mm. vs. 531,000 per cu. mm.), while Ottis (1952) noted that female golden hamsters had more platelets than males (742,000 per cu. mm. vs. 688,000 per cu. mm.).

Didisheim (1959) conducted a study of the coagulation properties of blood from eight mammalian and two avian species. While this study was designed to compare the clotting and coagulation factors, it also pointed out the fact that the differences in platelet function are relatively insignificant among mammals.

In 1960, Woodside examined the carbohydrates of human and bovine platelets. He found the total bound carbohydrates of the human platelet to be 8.5% of the dry weight while for the bovine platelet it was 8.8% of the dry weight. Considerable glycogen was present in both, and the monosaccharides were nearly alike, in both kind and quantity.

Adelson (1960) reported on platelet survival in dogs and humans under normal and abnormal conditions such as a hypocoagulable state produced by dicumarol and a hypercoagulable condition induced by the injection of epinephrine. He found the life span, production and destruction patterns were very similar in both species.

MEGAKARYOCYTES

A study of the platelet necessitates at least a survey of the megakaryocyte, which Wright (1910) proved to be the source of the platelets.

The megakaryocyte was named by Howell (1890) when he observed a teased out cell which was surrounded by vesicle-like bodies which were secreted by the large cell. Since the material dissolved in the plasma, Howell believed that it may have been utilized for nourishment of the blood-forming cells. While this work of Howell's was concerned with the function of the giant cells of the marrow, he unwittingly published an account of platelet production and utilization.

Early workers variously believed blood platelets to be precipitates from the plasma, extrusion products of the red corpuscles, fragmentation products of leukocytes, formed from the lymph follicles via fragmentation, precursors of red corpuscles, or a definite and independent type of cell (Wright 1910; Bedson 1923). The last of these was proven to be correct by Wright (1910).

Confirming the findings of Wright, Bunting (1909) then went on to study the dynamics of platelet production by megalokaryocytes (sic). Both Wright and Bunting describe the process of platelet production as one in which the megakaryocytes extend pseudopodia into the blood vessels of the bone marrow where portions of the pseudopodia become detached and are carried into circulation.

The process of megakaryocyte maturation has been examined by Rebuck (1947) and Digge (1962) who both view the process as taking place in four stages: a) Megakaryoblast which derives from the primitive hemocytoblast or reticulum cell, has a diameter of up to fifty microns, and a round or

bilobed nucleus. The cytoplasm is nongranular and basophilic. b) The promegakaryocyte is larger (up to eighty microns), the nucleus begins to divide, and the cytoplasm begins to show evidence of granulation, especially in the nuclear area. c) The early megakaryocytic form demonstrates numerous areas where the granules have begun to concentrate, leaving clearer areas of cytoplasm surrounding them. These granular clusters are often seen at the periphery of the cell in pseudopodial processes. d) The metamegakaryocyte, or dividing form of the megakaryocyte, exhibits demarcation membranes between the daughter nuclei, each of which assumes a dense form. These daughter nuclei to which the authors refer are actually the granular portions of the platelets, since the platelets do not have a nucleus.

Bond (1962), using tritiated thymidine in adult rats, was able to trace DNA synthesis in unrecognizable megakaryocyte precursors in the bone marrow. From calculations based on this procedure, he estimated the life span from the earliest recognizable megakaryoblast to megakaryocytic disintegration to be forty hours.

When Howell first observed megakaryocytic division in 1890, he believed it to be a direct (amitotic) division. However, Bond (1962) showed the synthesis of DNA in megakaryocytes, and Garcia (1964) using the histogram technique, presented evidence of a polyploid sequence from 2 N to 64 N, with lines at 16 N, 32 N, and 64 N to support the nearly simultaneous replication of chromosomal sets as could be expected in multipolar mitosis.

The location of the functioning megakaryocyte has been the subject of many investigations beginning with Howell (1937), when he found that in adult life the megakaryocytes are concentrated in the marrow and lungs, with the maximum of their activity in platelet production in the lungs.

Fidler (1941) refuted the observations of Howell, but offered no view of his own. Evidence to support the tenent of Howell was found by Scheinin (1962), when he sampled blood from the pulmonary artery and pulmonary veins of numerous humans with lung and chest pathology. He found a significant difference in the number of megakaryocytes entering and leaving the lungs, which he interprets as a sign of platelet production in the lungs.

Generally, the megakaryocytes are found in the fetus at about two and one half months, and may be found widely dispersed throughout the body (Sharnoff 1960). In later embryonic life they are more prevalent in the liver (Ackerman 1960) and lungs (Sharnoff 1960). In adults they are found in the bone marrow, spleen and lungs (Smith 1952; Bond 1962).

PLATELETS

Morphology The circulating platelet is a small, thin disc without processes (Zucker 1954). Electron microscopy reveals comparatively simple mitochondria, some granular bodies which may be derived from the mitochondria, and Golgi bodies, all in the central granulomere of the cytoplasm (Ferguson 1934; Rinehart 1955; Castaldi 1962). The surrounding hyalomere is distinct only in that it lacks any of the preceeding elements (Braunsteiner 1954). The membrane of the platelet is single and rather dense (Rodman 1962).

While the platelet is normally two to four microns in diameter and seven to eight cubic microns in volume (Olef 1937), Detwiler (1962) and McDonald (1964) reported that platelets decrease in size approximately twenty-five percent between youth and aged states.

Alterations in the shape of the platelet other than those associated with viscous metamorphosis and pathological conditions have been studied by Zucker (1954) while she was studying the effects of various anticoagulants. She found that morphological variations could be either permanent or reversible, and depended on temperature, osmotic pressure and type of anticoagulant used.

Chemical Character Research into platelet chemistry has only developed in the past decade and is still filled with doubts and conflicting reports.

The carbohydrate content of human platelets is 8.5% of the dry weight and consists of glycogen (Daniell 1959), a sulfated mucopolysaccharide believed to be chondroitin sulfate (Odell 1956), and numerous monosaccharides (Anderson 1953). The nitrogen content has been found to be 13.4% (Green 1954). Lipids present in platelets account for approximately 16% of their weight (Erickson 1939). Fractionation of the lipids has revealed five phospholipid components: lecithin, sphingomyelin, inositol, phosphatidylethanolamine and phosphatidylserine (Marcus 1958; Marcus 1960; Marcus 1961; Troup 1960; Woodside 1963).

Platelet enzymes are numerous (Koppel 1954; Marcus 1964; Zucker 1959a), although wide variations have been reported in quantitative studies (Geisler 1963), and in sites of activity (Koppel 1954).

Several investigators have examined antigens associated with platelets, and have found groups which can be differentiated as clearly as the ABO groups for erythrocytes (Baldini 1962). Ducos (1960) and Yunis (1963) believe that all blood group antigens which have been described for erythrocytes are present in platelets, while Ebbe (1961a; 1962b) goes further to include histocompatibility and platelet specific antigens also.

It has been demonstrated that platelets are able to actively bind substances such as serotonin, histamine, epinephrine and norepinephrine (Sano 1959a; Sano 1959b), but under physiological conditions it seems that only serotonin plays a constructive role in hemostasis (Sano 1959b). Additional substances are found adsorbed on the surface of the platelet, and some workers consider this adsorption to be an active metabolic process (Hjort 1955; Adelson 1960).

Enumeration Platelet counts may be made by direct or indirect methods or a combination of these, depending upon the laboratory preference. The two most widely used direct methods are those of Rees and Ecker (1923) and Brecher (1953). These involve an actual count of the platelets in a hemocytometer, and for the Brecher technique, a phase contrast microscope. The indirect methods in use are those of Dameshek (1932) and Olef (1935), which are basically the same, in that they both involve determination of the platelet-red corpuscle ratio, then the enumeration of the erythrocytes in a hemocytometer. Variations of the preceeding techniques have been used to find the platelet volume (Olef 1937) and the relative proportions as to size (Olef 1936; Arensburger 1955).

The figures for platelet counts in humans must be viewed cautiously since such wide ranges have been reported, partly due to techniques and possibly due to the site from which the sample was obtained. Rees and Ecker (1923) report an average count of 240,000 per cu. mm. The Brecher-Cronkite method (1953) yields counts which average 250,000 per cu. mm. Arensburger (1955) reports a mean of 310,000 per cu. mm. The "normal" ranges for these procedures all go from 140,000 up to 340,000 or 440,000 per cu. mm. For the indirect method of Dameshek (1932) the range is from 500,000 to 900,000 per cu. mm., while Olef (1932) found a mean of 514,000 per cu. mm., with extremes of 437,000 and 586,000 per cu. mm.

Changes in platelet numbers have been found to be related to various factors. Elevated platelet counts have been noted following surgery and fractures (Williams 1957), following strenuous exercise and relocation to a higher altitude (Tocantins 1938). Decreased platelet levels have been reported to obtain during the fourteen days prior to the onset of menstruation, with a return to normal after the onset (Pohle 1939). No significant changes have been reported in the platelet count during normal pregnancy other than a slight decrease during the first stage of labor and during the first two days postpartum (Jennings 1963).

Life Span of Platelets Estimates of platelet life span have been based on radioisotope labeling in three procedures: 1) the rate of platelet regeneration in animals made thrombocytopenic (Duke 1911; Kliman 1961); 2) length of survival of labeled platelets (Loeksma 1956; Adelson 1957); and 3) the length of time after whole body irradiation until the platelets disappeared from the peripheral circulation (Lawrence 1947; Craddock 1955; Odell 1961b).

Of these three, the length of platelet survival has been the most widely used. The preferred technique is to inject the label into a donor, then "harvest" the labeled platelets after a suitable time for incorporation and fixation of the label, then inject the platelets into a recipient and follow the radioactivity level in platelet aliquots (Adelson 1957).

While there is no "correct" method prescribed for determination of the life span, certain pitfalls must be avoided if the results are to be meaningful. Some attempts at in vitro labeling were in error since the excessive handling of the platelets seems to have damaged them (Mueller 1953). Heyssel (1961) used C^{14} serotonin as a label, but his later work in 1962,

corroborated by Zucker (1962), showed that serotonin could be exchanged between platelets and serotonin depots. This exchange was also noted by Grossman (1962), when he used P^{32} orthophosphate. The last and most unpredictable category of interferences includes the effects of drugs and the postoperative state (Adelson 1960a), and platelet isoimmunization (Cohen 1961).

The life span which seems most acceptable is in the realm of eight to nine days (Leeksma 1956; Adelson 1963), or nine to eleven days (Ans 1958).

Perhaps a more useful criterion for platelets would be the platelet viability index devised by Baldini (1960b) to compare the clot retraction ability of platelets, but this procedure needs standardization.

PLATELET DYNAMICS

Platelet Production While it has long been known that platelets derive from megakaryocytes, the factors regulating the production of both these cells has remained a question up to very recent times.

Fidlar (1941) suggested the possibility of a hormonal regulatory mechanism. Greer (1948) was unsuccessful in attempts to correlate adrenocorticotropin administration and levels of circulating platelets. Adams (1949) conducted a series of experiments in which he removed the adrenals, hypophysis and spleen from rabbits, mice and rats. His findings ruled out the adrenals and spleen as controlling factors, but showed some correlation between the hypophysis and the number of megakaryocytes in the bone marrow.

Three papers were published in 1951 dealing with idiopathic thrombocytopenic purpura, a disease in which there is an abundance of megakaryocytes in the bone marrow, yet a thrombocytopenic state obtains with no apparent

cause. The first suggests a humoral destructive mechanism (Stefanini); the second, by Evans, suggests that an immune reaction is the basis for this illness; while Harrington demonstrated a thrombocytopenic factor in the plasma of most idiopathic thrombocytopenic patients he examined. These three authors propose some sort of destructive mechanism which maintains platelets at a reduced level, but has no suppressive effect on the megakaryocytes. Attacking the problem from another angle, Schulman (1960) found a factor in normal plasma which stimulates platelet production by the megakaryocytes. This factor was lacking in persons with chronic thrombocytopenia.

Using exchange transfusion, it was possible for Matter (1960) to reduce platelet levels to ten per cent of normal, and to follow the subsequent thrombopoiesis. After a latent period of two days, there was an increase of platelets in circulation, and a return to normal levels by the seventh day after the thrombopoiesis began. Odell (1961a) was also able to inject serum from platelet-depleted rats into normal rats and bring about a substantial increase in the platelet levels (up to 167% of normal). He postulated that the increase was due to a stimulatory agent in the donor serum. Odell (1962) experimented with several foreign agents such as soluble egg albumin and powdered glass to produce thrombocytosis. These materials did promote platelet production, and the serum from these animals was also effective in increasing platelet production in recipients.

Once the serum was shown to contain thrombopoietic abilities, fractionation was undertaken by several persons; the work of Cheng (1962) and Steinberg (1962) seem to be the most noteworthy. These two papers present

almost identical results, inasmuch as both authors found separate megakaryocyte and platelet regulators which are associated with components of serum albumin.

While many workers were turning to chemical methods for platelet control mechanisms, a few were still utilizing the biological approach. Williams (1957) ruled out the corticoid responses to stress as affecting platelet level and production; Sharnoff (1960) suggested that stress might stimulate the right ventricle to act upon the megakaryocytes in the lungs and thus increase the number of platelets; and Cooney (1962) was able to extract a protein-rich substance from bovine spleens which elevated platelet levels of mice and rabbits without any change in the megakaryocyte numbers.

Odell (1964) published a review of the recent progress in platelet production factors along with the conclusion that there are natural humoral agents and secondary processes which respond to foreign agents.

Platelet Removal The factors relating to the fate of platelets, other than their consumption in blood coagulation, may be discussed in four main categories: 1) external factors; 2) deposition on the endothelium; 3) immune processes; 4) senescence.

Manipulation of the external factors has been accomplished by diet (Orma 1959; Mustard 1962b), oral and injectable administration of substances such as heparin and warfarin (Adelson 1963), thrombin (DeRobertis 1953), endotoxin (Duke 1912; Roy 1962), and india ink (Salvidio 1960); and smoking (Mustard 1962b). Of the preceeding, the dietary factors give variable results; the effect of drugs depends somewhat upon dosage; thrombin exerts a lytic effect upon platelets; and smoking results in a shortened platelet survival time for an unexplained reason.

Cronkite (1957) proposed that intact platelets or a sulfa-rich macromolecule from platelets played a part in lining small vessels, thereby aiding in maintenance of endothelial integrity. In his examination of endothelial membranes from the aorta and coronary arteries of swine, Mustard (1962b) found thrombi which had become covered with endothelium and incorporated into the intima.

The evidence for implication of platelets in immune responses has become strong in recent years largely due to work by Stefanini and co-workers (1952) who first detected an agglutinin in the serum of patients with hypoplastic anemia. Later work by this same group (1953a) showed this agglutinin to be a beta-globulin which interfered with the functional activity of platelets. However, Tullis (1956) found this platelet antibody to be a gamma-globulin. Further work by Stefanini (1953b) revealed the presence of two naturally occurring platelet agglutinins in humans. Schulman (1961) noted that an isoagglutinin provoked by a mismatched platelet antigen destroyed platelets in sensitized individuals.

From the scant amount of literature on the subject of platelet senescence, it seems that this topic has been the subject of more armchair biology than actual study. Olef (1936) stated that older platelets were larger, while Detwiler (1962) believed that older platelets decrease in size and clot retracting ability, but that there is no appreciable ATP decrease accompanying the aging process. What changes take place in the platelet as it ages if any, are still the subject of controversy.

Stefanini (1951b) stated that the spleen played no role in platelet survival time nor sequestration, although Vazquez (1960) supported the

sequestration of platelets in the spleen of patients with idiopathic thrombocytopenic purpura. In a comprehensive study, Aster (1964a; 1964b) showed that platelet removal occurs in the spleen when the platelets are "loaded" with relatively small amounts of isoantibody, while the heavily-laden platelets are removed and quickly destroyed in the liver. He believed this pattern of destruction obtains under normal conditions.

PLATELET FUNCTION

The primary functions of the platelet are hemostasis and synaresis. While the platelets may be found associated with coagulation, numerous workers have produced platelet-free clots (Howell 1914; Marcus 1958; Troup 1960).

In fulfilling their role in hemostasis, the platelets exhibit three properties: 1) adhesiveness, 2) aggregation, and 3) agglutination. Ferguson (1934) described the adherence of platelets to a foreign substance with the subsequent morphologic changes from spherical to stellate. The time required for a platelet to adhere to an abnormal surface was found to be one to two seconds (O'Brien 1963). Since the adherance of platelets to a foreign surface is virtually an instantaneous process, it may be a physical rather than a chemical reaction (Spaet 1962). Spaet later (1963) proposed the adhesion to be due to an alteration of the membrane, such as a realignment of the phospholipid molecules and the release of certain platelet contents. One of the substances released could be ADP, which has been shown to cause aggregation of platelets (Mustard 1964; Davey 1964). Another adhesion-promoting substance is connective tissue (Zucker 1962). As the form of the individual platelets becomes altered, a point is reached

at which separate platelets are no longer distinct due to fusion or agglutination (Zucker 1949; Kjaerheim 1962).

Upon contacting a wetable supporting surface, numerous pseudopode form after a few seconds and the granulomeres move into the center. After a few minutes the hyalomere spreads into a thin layer and disintegrates, leaving the granulomere which has coalesced, to form the retraction center of the fibrin net (Ferguson 1934; Braunsteiner 1954; Castaldi 1962; Rodman 1962). This process has been named viscous metamorphosis and may be related to the release of some platelet factor, such as lipid or serotonin, which is involved in hemostasis (Castaldi 1962).

It has been shown by Quick (1947) and Ware (1948) that platelets are concerned with the total conversion of prothrombin to thrombin, and to a lesser degree with the speed of this reaction (Ware 1948). Quick (1947) visualizes the process as one in which the platelets activate a thromboplastin precursor which in turn, along with calcium, will convert prothrombin to thrombin.

The second broad aspect of platelet function, syneresis or spontaneous retraction of a clot, has been examined from many angles since it was first delineated by Tocantins (1934). In 1936, Tocantins described the formation of fibrin needles with the platelets attached to them "resembling rain drops on a telegraph wire." The platelets which he viewed then proceeded to undergo viscous metamorphosis. At the same time the fibrin needles became beat, twisted and more closely knit. While Tocantins noted that the platelets must be intact and capable of agglutination to produce syneresis, he did not propose the means of accomplishing this. Zucker (1949) produced small puncture wounds which were later excised in toto, fixed, sectioned

and stained. He found fibrin strands in the central portions of the wounds, with a mixture of fibrin and platelets near the margins. In a similar procedure performed on arterioles of rabbit mesentery, Kjaerheim (1962) found that the platelets produced plugs which had some fibrin strands near the surface but none in the interior; therefore, he disagreed with the belief of Howell (1914) that fibrin forms a rigid meshwork.

Since it has been shown that the platelets are responsible for syneresis, the next question to be considered is how this occurs. Stefanini (1953c) suggested, since intact platelets are required for syneresis, that there might be some specific component in the hyalomere which is necessary. Jackson (1959) qualified Stefanini's theory to include viable platelets only, and later Detwiler (1962) conducted a study which revealed that clot retracting ability decreased with platelet age. He theorized that this reduction might be due to an impairment of the platelet's ability to metabolize glucose for ATP production. O'brien (1963) reported that platelets contain as much ATP as a muscle cell, and that thrombin catalyzes the conversion of ATP to ADP. Thus, with this finding by O'Brien, we have an energy source and a catalyst to give us a means of accomplishing the "work" which the platelets perform. Work by Conley (1960) demonstrated that platelets play an active role in clot retraction. The morphological changes associated with viscous metamorphosis are believed to be intimately associated with the contraction of fibrin strands, but Conley was unable to explain the exact chemical or biological reactions.

Secondary functions which have been ascribed to platelets include the maintenance of vascular integrity (Hirsch 1951; Cronkite 1957); the adhesion to foreign substances such as bacteria, endotoxin and india ink (Salvidio 1960; Roy 1962); and the adsorbance of vasoconstrictive substances (Sano 1951a).

PLATELET PATHOLOGY

The pathological conditions associated with platelets are few in number and largely unexplained. While the descriptions which will follow will be categorized as to quantitative, qualitative and morphologic abnormalities, there is always some occasion for the overlap of multiple conditions.

Quantitative Thrombocythemia is the condition in which there is an abnormally high platelet count for an extended period of time, as opposed to temporary conditions which may be accompanied by thrombocytosis. Thrombocythemia, a rare condition, is sometimes seen in conjunction with chronic myelocytic leukemia (Minot 1925) and erythremia (Dameshek 1940). The highest platelet counts found were in the range of 3,000,000 to 6,000,000 per cu. mm. (Dameshek 1940). It is not known if there is any qualitative platelet abnormality associated with thrombocythemia.

Transient thrombocytosis, often associated with the presence of many small easily agglutinating platelets, has been found in infectious diseases (Olef 1936) and following surgery (Williams 1957).

The literature dealing with thrombocytopenic states is voluminous and ranges from naturally occurring thrombocytopenic purpura to experimentally induced thrombocytopenia. While purpura hemorrhagica has long been known as an affliction of man, Duke (1912) was the first to quantify the disease when he noted that 40,000 platelets per cu. mm. seemed to be the point below which bleeding tendency is noted.

Primary thrombocytopenic purpura and idiopathic thrombocytopenic purpura are the two most common names for the syndrome characterized by a thrombocytopenic state developing in the absence of any apparent underlying disorder, and accompanied by an abundance of megakaryocytes in the bone

marrow (Schulman 1961). The mechanism of bleeding in this disease is known only in part: 1) the coagulation defect is associated with deficiency of a platelet enzyme necessary to enhance the conversion of prothrombin to thrombin (Quick 1947); 2) there is poor clot retraction, with decrease in adhesiveness, rigidity and contractility of the clot (Quick 1947); and 3) there is apparent failure to form a platelet plug in severed blood vessels (Zucker 1949).

The initiating cause is unknown. Many patients with this disorder have a substance in their circulating blood plasma capable of agglutinating normal platelets and of producing thrombocytopenic purpura upon transfusion into normal human subjects (Harrington 1951; Stefanini 1953a). Early work into the nature of the causative agent led to the discovery that thrombocytopen, which could be extracted from the liver and/or spleen of patients with idiopathic thrombocytopenic purpura, would reduce the number of platelets in the circulating blood of rabbits (Troland 1938; Otenasek 1941; Rose 1941). Later workers tried to relate decreased platelet production (Dameshek 1946), and accelerated platelet destruction (Stefanini 1951), both under humoral control, as the primary cause of idiopathic thrombocytopenic purpura. The fact that the antiplatelet plasma factor is an antibody was proposed by Evans (1951), then categorized into groups by Stefanini (1953b), and found to be a gamma globulin by Stefanini (1953a) and Tullis (1956). Dausset (1961) felt that the gamma globulin may actually emit from the platelets themselves, although this seems to be somewhat speculative.

The pathogenesis of idiopathic thrombocytopenic purpura has been variously proposed as a virus infection which was responsible for the development of a hetero-platelet agglutinin, or an effect of the active lytic processes of red cells and platelets (Adelson 1952), and finally, as a result of widespread

intravascular coagulation with the deposition and accumulation of precipitated fibrin (Taub 1963).

The relation of the spleen to this disease remains obscure and the relief occasioned by splenectomy has not been satisfactorily explained (Harrington 1951; Stefanini 1951; Stefanini 1953a; Schulman 1960). Temporary relief of bleeding tendency may be obtained by transfusion of platelet-rich blood (Hirsch 1951; Hirsch 1952; Jackson 1959).

Secondary or symptomatic thrombocytopenic purpura is characterized by the reduction of platelets due to involvement of the bone marrow by infiltration with foreign cells (Wintrobe 1933) or tissues (Zucker 1959b); by hypoplasia or even complete aplasia due to irradiation (Lawrence 1947; Craddock 1955); by drug intoxications as with heparin (Fidlar 1948), or dextran (Stetson 1951; Adelson 1955; Langdell 1955; Rose 1959); endotoxin (Roy 1962); and india ink (Salvidio 1960).

Qualitative Deficiencies in platelet function are grouped under the heading of thrombocytopathy (Braunsteiner 1956). A reduction in the quality of the platelets as in thrombasthenic purpura or Glanzmann's thrombasthenia is very rare. This disease is characterized by a normal platelet count, bleeding time and coagulation time, but a possible structural defect (vacuolization) and abnormal pseudopod formation upon contacting a wetable surface (MacFarlane 1941; Braunsteiner 1956).

While a hypercoagulable state has been exhibited by various workers due to stress (Cannor 1914c; Friedman 1958; DeLong 1959), diet (Uhley 1959; Connor 1962) and drugs (Cannon 1914a; Cannon 1914b; Weiner 1948), platelets have been implicated only to the extent that during thrombic states there are an increased number of small, easily agglutinating platelets (Olef 1936),

which provide a relatively large surface area for the transport of accessory clotting factors (Tocantins 1938; Sano 1959a; Sano 1959b).

Morphologic Accompanying idiopathic thrombocytopenic purpura and leukemia, large atypical, nongranular platelets which have been dubbed "giant platelets" may be seen (Rebuck 1947; Lewis 1957). Platelets lacking cytoplasm are found during periods of active regeneration (Bunting 1911). Braunsteiner (1954) reported that platelets exhibiting defective pseudopod formation were seen in the presence of exogenous platelet damaging agents, and were possibly due to an inherent defect in the platelets which he was unable to identify.

Acknowledgement

The author wishes to express a sincere appreciation to Assistant Professor Charles H. Lockhart of the Department of Zoology for his invaluable assistance as counselor and teacher.

BIBLIOGRAPHY

Aas, K. A. and Gardner, F. H.
Survival of blood platelets labeled with chromium. J. Clin. Invest. 37: 1257-1268, 1958.

Ackerman, G. A. and Knouff, R. A.
Histochemical differentiation of the megakaryocytes in the embryonic liver. Blood, 15: 267-276, 1960.

Adams, E.
Observations on the influence of the hypophysis and the adrenal cortex on blood platelet levels. Blood, 4: 936-946, 1949.

Adelson, E. and Stefanini, M.
Studies on platelets. VI. Demonstration and characterization of a heterologous (Forsman) platelet agglutinin. Blood, 7: 700-709, 1952.

Adelson, E., Crosby, W. H. and Roeder, W. H.
Further studies of a hemostatic defect caused by intravenous dextran. J. Lab. & Clin. Med. 45: 441-448. 1955.

Adelson, E., Rheingold, J. J. and Crosby W. H.
Studies of platelet survival by tagging in vivo with P^{32}. J. Lab. & Clin. Med. 50: 570-576, 1957.

Adelson, E., Rheingold, J. J., Parker, C., Buenaventura, A. and Crosby, W. H.
Platelet and fibrinogen survival in normal and abnormal states of coagulation. Blood, 17: 267-281, 1960a.

Adelson, E., Rheingold, J. J. and Crosby, W. H.
The platelet as a sponge: A review. Blood, 17: 767-774, 1960b.

Adelson, E., Kaufman, H. M., Lear, A. A., Kirby, J. C. and Rheingold, J. J.
Physiology of platelet destruction as revealed by tagging of cohorts. I. Studies in dogs. J. Lab. & Clin. Med. 62: 385-393, 1963.

Anderson, B. and Odell, T. T., Jr.
Chemical studies of mucopolysaccharides of rat blood platelets. Proc. Soc. Exper. Biol. & Med. 99: 765-768, 1958.

Arensburger, K. E.
A modified direct method for enumeration & study of platelets. Am. J. Clin. Path. 25: 1220-1223, 1955.

Aster, R. H. and Jandl, J. H.
Platelet sequestration in man. I. Methods. J. Clin. Invest. 43: 843-855, 1964a.

Aster, R. H. and Jandl, J. H.
Platelet sequestration in man. II. Immunological and clinical studies. J. Clin. Invest. 43: 856-869, 1964b.

Baldini, M., Costea, N. and Dameshek, W.
The viability of stored human platelets. Blood, 16: 1669-1692, 1960.

Baldini, M., Ebbe, S. and Bridges, J. M.
Isoimmunity to blood platelets. Blood, 20: 761, 1962.

Bedson, S. P.
An enquiry into the genesis of the mammalian blood platelet. J. Path. & Bact. 26: 145-155, 1923.

Bond, V. P., Feinendegen, L. E., Odartchenko, N. and Cottier, H.
Kinetics of megakaryocyte proliferation in rat bone marrow. Blood, 20: 767, 1962.

Braunsteiner, H., Pellinger, K. and Pakesch, F.
Structural changes in the platelets as observed by electron microscopy. Blood, 9: 595-601, 1954.

Braunsteiner, H. and Pakesch, F.
Thrombocytoasthenia and thrombocytopathia - Old names and new diseases. Blood, 11: 965-976, 1956.

Brecher, G., Schneiderman, M. and Cronkite, E. P.
The reproducibility and constancy of the platelet count. Am. J. Clin. Path. 23: 15-26, 1953.

Bunting, C. H.
Blood-platelet and megalokaryocyte relations in the rabbit. J. Exper. Med. 11: 541-552, 1909.

Bunting, C. H.
Blood platelets and megalokaryocytes in Hodgkin's disease. Bull. Johns Hopkins Hosp. 22: 114-116, 1911.

Cameron, D. G. and Watson, G. M.
The blood counts of the adult albino rat. Blood, 4: 816-818, 1949.

Cannon, W. B. and Gray, H.
Factors affecting the coagulation of blood. II. The hastening or retarding of coagulation by adrenalin injections. Am. J. Physiol. 34: 232-242, 1914a.

Cannon, W. B. and Gray, H.
Factors affecting the coagulation of blood. II. The hastening or retarding of coagulation by adrenalin injections. Am. J. Physiol. 34: 243-250, 1914b.

Cannon, W. B. and Mendenhall, W. L.
Factors affecting the coagulation time of blood. IV. The hastening of coagulation in pain and emotional excitement. Am. J. Physiol. 34: 251-261, 1914c.

Casey, A. E., Rosahn, P. D., Hu, Ch'Uan-K'Uan and Pearce, L.
The hemocytological constitution of adult male rabbits from fifteen standard breeds. J. Exper. Med. 64: 453-470, 1936.

Castaldi, P. A., Fukin, B. G., Blackwell, P. M. and Clifford, K. I.
An electron microscopic study of the changes in platelets during viscous metamorphosis. Blood, 20: 566-580, 1962.

Cheng, F. H. and Steinberg, B.
Chemical separation and properties of platelet regulators. Blood, 20: 770, 1962.

Cohen, P., Gardner, F. H. and Barnett, G. O.
Reclassification of the thrombocytopenias by the Cr^{51} labeling method for measuring platelet life span. N. E. J. Med. 264: 1294-1299 and 1350-1355, 1961.

Conley, C. L.
Platelets in clot retraction, p 437-444, in Blood Platelets: Henry Ford Hospital International Symposium, S. Johnson, Ed. Boston, Little, Brown & Co., 1961.

Connor, W. E.
The acceleration of thrombus formation by certain fatty acids. J. Clin. Invest. 41: 1199, 1962.

Cooney, D. P. and Blatt, W. F.
Studies on thrombopoiesis: Effect of non-dialyzable spleen extract on the blood platelet level. Blood, 20: 769, 1962.

Craddock, C. G., Jr., Adams, W. S., Perry, S. and Lawrence, J. S.
The dynamics of platelet production as studied by a depletion technique in normal and irradiated dogs. J. Lab. & Clin. Med. 45: 906-919, 1955.

Cronkite, E. P., Bond, V. P., Robertson, J. S. and Paglia, D. E.
The survival, distribution and apparent interaction with capillary endothelium of transfused radiosulfate labeled platelets in the rat. J. Clin. Invest. 36: 881, 1957.

Dameshek, W.
A method for the simultaneous enumeration of blood platelets and reticulocytes. Arch. Int. Med. 50: 579, 1932.

Dameshek, W. and Henstell, H. H.
The diagnosis of polycythemia. Ann. Int. Med. 13: 1360, 1940.

Dameshek, W. and Miller, E. B.
The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism. Blood, 1: 27-50, 1946.

Daniell, H. W.
Studies of megakaryocyte glycogen. I. A semiquantitative method of measurement: Effect of phlebotomies in young adults. Blood, 14: 60-73, 1959.

Davey, M. G. and Landen, H.
Effect of adenosine diphosphate on circulating platelets in man. Nature, 201: 1037-1039, 1964.

Dausset, J., Colombani, J. and Colombani, M.
Study of the leukopenias and thrombocytopenias by the direct anti-globulin consumption test on leukocytes and/or platelets. Blood, 18: 672-690, 1961.

DeLong, E., Uhley, H. N. and Friedman, M.
Changes in blood clotting time of rats exposed to a particular form of stress. Am. J. Physiol. 196: 429-430, 1959.

DeRobertis, E., Paseyre, P. and Reissig, M.
Electron microscopic studies of the action of thrombin on blood platelets. Blood, 7: 587-597, 1953.

Detwiler, T. C., Odell, T. T. Jr. and McDonald, T. P.
Platelet size, ATP content and clot retraction in relation to platelet age. Am. J. Physiol. 203: 107-110, 1962.

Didisheim, P., Hattori, K. and Lewis, J.
Hematologic and coagulation studies in various animal species. J. Lab. & Clin. Med. 53: 866, 1959.

Diggs, L. W.
Morphology of megakaryocytes. Blood, 20: 767, 1962.

Duces, J., Brousay, J. and Ruffie, J.
Kell antigen in human platelets. Rev. Fr. Et. Clin. Biol. 4: 370, 1959. Abstract in Blood, 15: 571, 1960.

Duke, W. W.
The relation of blood platelets to hemorrhagic disease. J. A. M. A. 55: 1185, 1910.

Duke, W. W.
The rate of regeneration of blood platelets. J. Exper. Med. 14: 265-273, 1911.

Duke, W. W.
The pathogenesis of purpura hemorrhagica with especial reference to the part played by blood platelets. Arch. Int. Med. 10: 445-469, 1912.

Ebbe, S., Baldini, M. and Dameshek, W.
The antigenic structure of blood platelets. I. Demonstration in the rabbit of antigens in common between skin and blood platelets. Blood, 19: 537-547, 1961a.

Ebbe, S., Baldini, M. and Dameshek, W.
The antigenic structure of blood platelets. II. Histocompatibility antigens in rabbit blood platelets. Blood, 19: 548-556, 1961b.

Erickson, B. N., Williams, H. H., Arvin, I. and Lee, P.
The lipid distribution of human platelets in health and disease. J. Clin. Invest. 18: 81-85, 1935.

Evans, R. S. and Kong, C.
Effect of corticotrophin on chronic, severe primary thrombocytopenic purpura. A. M. A. Arch. Int. Med. 88: 503-506, 1951.

Ferguson, J. H.
Observations on the alterations of blood platelets as a factor in the coagulation of the blood. Am. J. Physiol. 108: 670-682, 1934.

Fidlar, E. and Waters, E. T.
The origin of platelets. Their behavior in the heart-lung preparation. J. Exper. Med. 73: 299-307, 1941.

Fidlar, E. and Jaques, L. B.
The effect of commercial heparin on the platelet count. J. Lab. & Clin. Med. 33: 1410-1423, 1948.

Forkner, C. E.
Blood and bone marrow cells of the domestic fowl. J. Exper. Med. 50: 121-141, 1929.

Friedman, M., Rosenman, R. H. and Carroll, V.
Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress. Circulation, 17: 852-861, 1958.

Garcia, A. M.
Feulgen-DNA values in megakaryocytes. J. Cell. Biol. 20: 342-345, 1964.

Geisler, P. H., Iossifides, I. A. and Eichman, M. F.
Preservation of the lactic dehydrogenase activity of platelets by freezing in Dimethylsulfoxide and plasma. Blood, 24: 761-762, 1963.

Greer, M. A. and Brown, B. R.
Concerning the relation between pituitary adrenocorticotrophin and the circulating blood platelets. Proc. Soc. Exper. Biol. & Med. 69: 361-362, 1948.

Grossman, C. M., Kohn, R. and Koch, R.
Possible errors in the use of P^{32} orthophosphate for the estimation of platelet life span. Blood, 22: 9-15, 1962.

Harrington, W. J., Minnich, V., Hollingsworth, J. W. and Moore, C. V.
Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. J. Lab. & Clin. Med. 38: 1-10, 1951.

Heyssel, R. M.
Determination of human platelet survival utilizing C^{14} labelled Serotonin. J. Clin. Invest. 40: 2134-2142, 1961.

Heyssel, R. M., Brill, A. B. and Moore, H.
Further experience with C^{14} 5-hydroxytryptamine platelet survival data. Blood, 20: 763, 1962.

Hirsch, E. O. and Gardner, F. H.
The life span of transfused human platelets. J. Clin. Invest. 30: 649-650, 1951.

Hjort, P., Rapaport, S. I. and Owren, P. A.
Evidence that platelet accelerator (Platelet factor I) is adsorbed plasma proaccelerin. Blood, 10: 1139-1150, 1955.

Howell, W. H.
Observations upon the occurrence, structure, and function of the giant cells of the marrow. J. Morphol. 4: 117-130, 1890.

Howell, W. H.
The clotting of blood as seen with the ultramicroscope. Am. J. Physiol. 35: 143-149, 1914.

Howell, W. H. and Donahue, D. D.
The production of blood platelets in the lungs. J. Exper. Med. 65: 177-203, 1937.

Jackson, D. P., Sorenson, D. K., Cronkite, E. P., Bond, V. P. and Fliedner, T. M.
Effectiveness of transfusions of fresh and lyophilized platelets in controlling bleeding due to thrombocytopenia. J. Clin. Invest. 38: 1689-1697, 1959.

Jennings, J. A.
Thromboembolytic disease in obstetrics and gynecology. Henry Ford Hosp. Med. Bull. 11: 289-307, 1963.

Jordan, H. E.
The evolution of blood-forming tissues. Quart. Rev. Biol. 8: 58-76, 1933.

Kjaerheim, A. and Hovig, T.
Hemostatic blood platelet plugs in rabbits. J. Ultrastructure Res. 6: 138-139, 1962.

Klinman, A., Gaydos, L. A., Schroeder, L. R. and Freireich, E. J.
Repeated plasmapheresis of blood donors as a source of platelets.
Blood, 18: 303-309, 1961.

Koppel, J. L. and Owlin, J. H.
Dehydrogenase activities of human platelets. Proc. Soc. Exper. Biol. & Med. 86: 641-645, 1954.

Langdell, R. D., Adelson, E., Furth, F. W. and Crosby, W. H.
Dextran and prolonged bleeding time. Results of a sixty-gram one-liter infusion given to one hundred sixty-three normal human subjects.
J. A. M. A. 166: 346-351, 1958.

Lawrence, J. S. and Valentine, W. N.
The blood platelet: The rate of their utilization in the cat. Blood, 2: 40-49, 1947.

Leeksma, C. H. W. and Cohen, J. A.
Determination of the life span of human blood platelets using labeled diisopropylfluorophosphonate. J. Clin. Invest. 35: 964-969, 1956.

Lewis, J. H., Burchenal, J. H., Ellison, R. L., Ferguson, J. H., Palmer, J. H., Murphy, M. L. and Zucker, M. B.
Studies of hemostatic mechanisms in leukemia and thrombocytopenia.
Am. J. Clin. Path. 28: 433-446, 1957.

McDonald, T. P., Odell, T. T., Jr. and Gosslee, D. G.
Platelet size in relation to platelet age. Proc. Soc. Exper. Biol. & Med. 115: 684-689, 1964.

MacFarlane, R. G.
Critical review: The mechanism of hemostasis. Quart. J. Med. 10: 1-29, 1941.

Marcus, A. J. and Spaet T. H.
Platelet phosphatides: Their separation, identification and clotting activity. J. Clin. Invest. 37: 1836-1845, 1958.

Marcus, A. J., Ullman, H. L. and Wolfman, M.
Studies on blood platelet phospholipids. J. Lipid. Res. 1: 179, 1960.

Marcus, A. J., Ullman, H. L. and Ballard, H. S.
Fatty acids of human platelet phosphatides. Proc. Soc. Exper. Biol. & Med. 107: 483-486, 1961.

Marcus, A. J. and Zucker-Franklin, D.
Enzyme and coagulation activity of subcellular platelet fractions.
J. Clin. Invest. 43: 1241-1242, 1964.

Matter, M., Hartman, J. R., Kautz, J., DeMarsh, Q. B. and Finch, C. A.
A study of thrombopoiesis in induced acute thrombocytopenia. Blood, 15: 174-185, 1960.

Mayersen, H. S.
The blood cytology of dogs. Anat. Rec. 47: 239-250, 1930.

Minot, G. R. and Buckman, T. E.
The blood-platelets in the leukemias. Am. J. M. Sc. 169: 477-485, 1925.

Mueller, J. F.
Pathological physiology of mammalian blood platelets utilizing P^{32} tagged rabbit platelets. Proc. Soc. Exper. Biol. & Med. 83: 557-561, 1953.

Mustard, J. F. and Murphy E. A.
Blood platelet economy during moderate and intensive therapy. Blood, 22: 1-8, 1962a.

Mustard, J. F., Geissinger, H. D., Robinson, G. A., Rowsell, H. C., Murphy, E. A., McCarter, M. and Riddell, P.
Factors influencing the fate of the platelet. Blood, 20: 765, 1962b.

Mustard, J. F., Hegardt, B. H., Rowsell, H. C. and MacMillan, R. L.
Effect of adenosine nucleotides on platelet aggregation and clotting time. J. Lab. & Clin. Med. 64: 548-559, 1964.

O'Brien, J. R.
The mechanism and prevention of platelet adhesion considered in relation to arterial thrombosis. Blood, 24: 309-314, 1963.

Odell, T. T., Jr. and Anderson, B.
Isolation of a sulfated mucopolysaccharide from blood platelets of rats. Proc. Soc. Exper. Biol. & Med. 94: 151-156, 1956.

Odell, T. T., Jr., McDonald, T. P. and Detwiler, T. C.
Stimulation of platelet production by serum of platelet-depleted rats. Proc. Soc. Exper. Biol. & Med. 108: 428-431, 1961a.

Odell, T. T., Jr.
Platelet labeling with radioisotopes and in vivo platelet survival, pp 643-649, in Blood Platelets: Henry Ford Hospital International Symposium, S. Johnson, Ed. Boston, Little, Brown & Co., 1961b.

Odell, T. T., Jr. and McDonald, T. P.
Effects of various agents on blood platelet production. Blood, 20: 769, 1962.

Odell, T. T., Jr., McDonald, T. P. and Howsden, F. L.
Native and foreign stimulators for platelet production. J. Lab. & Clin. Med. 64: 418-424, 1964.

Olef, I.
The enumeration of blood platelets. J. Lab. & Clin. Med. 20: 416-436, 1935.

Olef, I.
The differential platelet count. Arch. Int. Med. 57:1163-1185, 1936.

Olef, I.
The determination of platelet volume. J. Lab. & Clin. Med. 23: 166-178, 1937.

Orma, E., Rhodes, D. N. and Keys, A.
Egg-containing meals and blood coagulation. Lancet, 2: 388, 1959.

Osler, W.
Resume of history of blood platelets. Bull. Johns Hopkins Hosp. 16: 200-201, 1905.

Otensek, F. and Lee, F. C.
Further observations on thrombocytopen. J. Lab. & Clin. Med. 26: 1266-1273, 1941.

Ottis, K. and Tauber, O. E.
Blood platelet counts of the Golden Hamster, Cricetus auratus. Blood, 7: 948-949, 1952.

Pohle, F. J.
The blood platelet count in relation to the menstral cycle in normal women. Am. J. Med. Sc. 197: 40-47, 1939.

Quick, A. J.
Studies on the enigma of the hemostatic dysfunction in hemophilia. Am. J. Med. Sc. 214: 272-280, 1947.

Rebuck, J. W.
The structure of the giant cells in the blood forming organs. J. Lab. & Clin. Med. 32: 660-699, 1947.

Rees, H. M. and Ecker, E. E.
An improved method for counting blood platelets. J. A. M. A. 80: 621-622, 1923.

Rinehart, J. F.
Electron microscopic studies of sectioned white blood cells and platelets. Am. J. Clin. Path. 25: 605-619, 1955.

Rodman, N. F., Jr., Mason, R. G., McDevitt, N. B. and Brinkhous, K. M.
Morphologic alterations of human blood platelets during early phases of clotting. Electron microscopic observations of thin sections. Am. J. Path. 40: 271-284, 1962.

Rose, H., Jr., and Boyer, L. B.
Thrombocytopen: A confirmatory report. J. Clin. Invest. 20: 81-86, 1941.

Ross, S. W. and Ebert, R. V.
Microelectrophoresis of blood platelets and the effects of dextran. J. Clin. Invest. 38: 155-159, 1959.

Roy, A. J., Djerassi, I., Neitlich, H. and Farber, S.
Effects of Escherichia coli endotoxin on rat platelets. Am. J. Physiol. 203: 296-298, 1962.

Salvidio, E. and Crosby, W. H.
Thrombocytopenia after intravenous injection of india ink. J. Lab. & Clin. Med. 56: 711-716, 1960.

Sano I., Kakimoto, Y. and Taniguchi, K.
Binding and transport of serotonin in rabbit blood platelets and action of reserpine. Am. J. Physiol. 195: 495-498, 1959a.

Sano, I., Kakimoto, Y., Taniguchi, K. and Takesasa, M.
Active transport of epinephrine into blood platelets. Am. J. Physiol. 197: 81-84, 1959b.

Scheinin, T. M. and Koineviemi, A. P.
Megakaryocytes in the pulmonary circulation. Blood, 22: 82-87, 1962.

Schulman, I., Pierce, M., Lukens, A. and Currimbhoy, Z.
Studies on thrombopoiesis. I. A factor in normal human plasma required for platelet production; chronic thrombocytopenia due to its deficiency. Blood, 16: 943-957, 1960.

Schulman, N. R., Aster, R. C., Leitner, A. and Hiller, M. C.
Immunoreactions involving platelets. V. Post-transfusion purpura due to a complement-fixing antibody against a genetically controlled platelet antigen. A proposed mechanism for thrombocytopenia and its relevance in "Autoimmunity". J. Clin. Invest. 40: 1597-1620, 1961.

Sharnoff, J. G. and Scardino, V.
Pulmonary megakaryocytes in human fetuses and premature and full-term infants. Arch. Path. 69: 139, 1960.

Shirakawa, M. and Lewis, J. H.
Premammalian thrombocytes. Blood, 20: 766-767, 1962.

Smith, E. B. and Butcher, J.
The incidence, distribution and significance of megakaryocytes in normal and diseased human tissues. Blood, 7: 214-224, 1952.

Spaet, T. H., Gintron, J. and Spivack, M.
Some properties of the platelet-connective tissue mixed agglutination reaction. Proc. Soc. Exper. Biol. & Med. 111: 292-295, 1962.

Spaet, T. H. and Gintron, J.
Studies on the responses of platelets to foreign surfaces. Blood, 24: 852, 1963.

Stefanini, M., Chatterjae, J. B., Dameshek, W., Zannos, L. and Santiago, E. P.
Studies on platelets. II. The effect of transfusion of platelet-rich polycythemic blood on the platelets and hemostatic function in 'Idiopathic' and 'Secondary' thrombocytopenic purpura. Blood, 7: 53-76, 1951a.

Stefanini, M. and Chatterjea, J. B.
Rate of platelet survival in thrombocytopenia. J. Clin. Invest. 30: 676, 1951b.

Stefanini, M., Dameshek, W. and Adelson, E.
Platelets: VII. Shortened 'Platelet survival time' and development of platelets agglutinins following multiple platelet transfusions. Proc. Soc. Exper. Biol. & Med. 80: 230-235, 1952.

Stefanini, M., Dameshek, W., Chatterjea, J. B., Adelson, E. and Mednicoff, I. B.
Studies on platelets. IX. Observations on the properties and mechanism of action of a potent platelet agglutinin detected in the serum of a patient with idiopathic thrombocytopenic purpura (with a note on the pathogenesis of the disease). Blood, 8: 26-64, 1953a.

Stefanini, M., Plitman, G. I., Dameshek, W., Chatterjea, J. B. and Mednicoff, I. B.
Studies on platelets. XI. Antigenicity of platelets and evidence of platelet groups in man. J. Lab. & Clin. Med. 42: 723-738, 1953b.

Stefanini, M.
Mechanism of blood coagulation in normal and pathological conditions. Am. J. Med. 14: 64-86, 1953c.

Steinberg, B. and Martin, R. A.
Thrombopoiesis. Blood, 20: 770, 1962.

Stetson, C. A.
The nature of blood vessel damage in the Schwartzman phenomenon. J. Clin. Invest. 30: 676-677, 1951.

Taub, R. N., Rodriquez-Erdmann, R. and Dameshek, W.
Intravascular coagulation, the Schwartzman reaction and the pathogenesis of idiopathic thrombocytopenic purpura. Blood, 24: 775-779, 1963.

Tocantins, L. M.
Platelets and the spontaneous syneresis of blood clots. Am. J. Physiol. 110: 278-286, 1934.

Tocantins, L. M.
Platelets and the structure and physical properties of blood clots. Am. J. Physiol. 114: 709-715, 1936.

Tocantins, L. M.
The mammalian blood platelet in health and disease. Medicine, 17: 155-260, 1938.

Tocantins, L. M.
Historical notes on blood platelets. Blood, 3: 1073-1082, 1948.

Troland, C. E. and Lee, F. C.
Thrombocytopen. J. A. M. A. 111: 221-226, 1938.

Troup, S. B., Reed, C. F., Marinetti, G. V. and Swisher, S. N.
Thromboplastic factors in platelets and red blood cells: Observations on their chemical nature and function in the in vitro coagulation. J. Clin. Invest. 39: 342, 1960.

Tullis, J. L.
Identification and significance of platelet antibodies. N. E. J. Med. 255: 541-551, 1956.

Vazquez, J. J. and Lewis, J. H.
Immunocytochemical studies on platelets. The demonstration of a common antigen in human platelets and megakaryocytes. Blood, 16: 968-974, 1960.

Ware, A. G., Fahey, J. L. and Seegers, W. H.
Platelet extracts, fibrin formation and interaction of purified prothrombin and thromboplastin. Am. J. Physiol. 154: 140-147, 1948.

Weiner, M., Zeltmacher, K., Reich, C. and Shapiro, S.
Platelet adhesiveness. Blood, 3: 1275, 1948.

Williams, J. A. and Warren, R.
Endocrine factors in the alteration of the blood coagulation mechanism following surgery. J. Lab. & Clin. Med. 50: 372-375, 1957.

Wintrobe, M. M. and Buell, M. V.
Hyperproteinemia associated with multiple myeloma. Bull. Johns Hopkins Hosp., 52: 156-165, 1933.

Woodside, E. E. and Kocholaty, W.
Carbohydrates of human and bovine platelets. Blood, 16: 1173-1183, 1960.

Woodside, E. E., Therriault, D. G. and Kocholaty, W.
Lipids of human platelets and their action on the blood coagulation process. Blood, 24: 76-91, 1963.

Wright, J. H.
The histogenesis of blood platelets. J. Morphol. 21: 263-278, 1910.

Yunis, E. J. and Yunis, J. J.
Cell antigens and cell specialization. IV. On the H blood group antigen of human platelets and nucleated cells of the human bone marrow. Blood, 24: 531-541, 1963.

Zucker, H. D.
Platelet thrombosis in human hemostasis. Blood, 4: 631-645, 1949.

Zucker, M. B. and Borrelli, J.
Reversible alterations in platelet morphology produced by anticoagulants and by cold. Blood, 9: 602-608, 1954.

Zucker, M. B. and Borrelli, J.
Platelets as a source of serum acid nitrophenylphosphatase. J. Clin. Invest. 38: 148-154, 1959a.

Zucker, M. B., Ley, A. B., Borrelli, J., Mayer, K. and Firmat, J.
Thrombocytopenia with a circulating platelet agglutinin, platelet lysin, and clot retraction inhibitor. Blood, 14: 148-161, 1959b.

Zucker, M. B., Zumoff, B. and Hellman, L.
Rapid exchange of platelet C^{14} labeled serotonin in patients with functioning carcinoid tumors. Blood, 20: 764, 1962.

GENESIS AND COMPARISON OF MAMMALIAN BLOOD PLATELETS

by

THOMAS EDWARD NIGHTINGALE

A. B., Kansas State University, 1964

AN ABSTRACT OF A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Zoology

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1966

Approved by:

Major Professor

This report is a compilation of literature dealing with the subject of mammalian blood platelets.

The report begins with a brief history of platelets from the time they were first publicly described until they were shown to be associated with hemorrhagic diseases. Then the platelets and their premammalian homologue, the thrombocyte are described and compared.

The origin of platelets from megakaryocytes is discussed, along with a review of the factors which have been proposed for megakaryocyte maturation and platelet production. Data concerning platelet morphology and chemical character is presented, along with resumés of studies from classic experimentally induced thrombocytopenia to the present era of radioisotope use to determine production, enumeration and life span of platelets.

An account of the role of platelets in hemostasis and syneresis during normal and abnormal conditions is presented. Quantitative and qualitative platelet dyscrasias are described. Since idiopathic thrombocytopenic purpura is the most common and best described platelet-related affliction of humans, this ailment is examined in some detail.