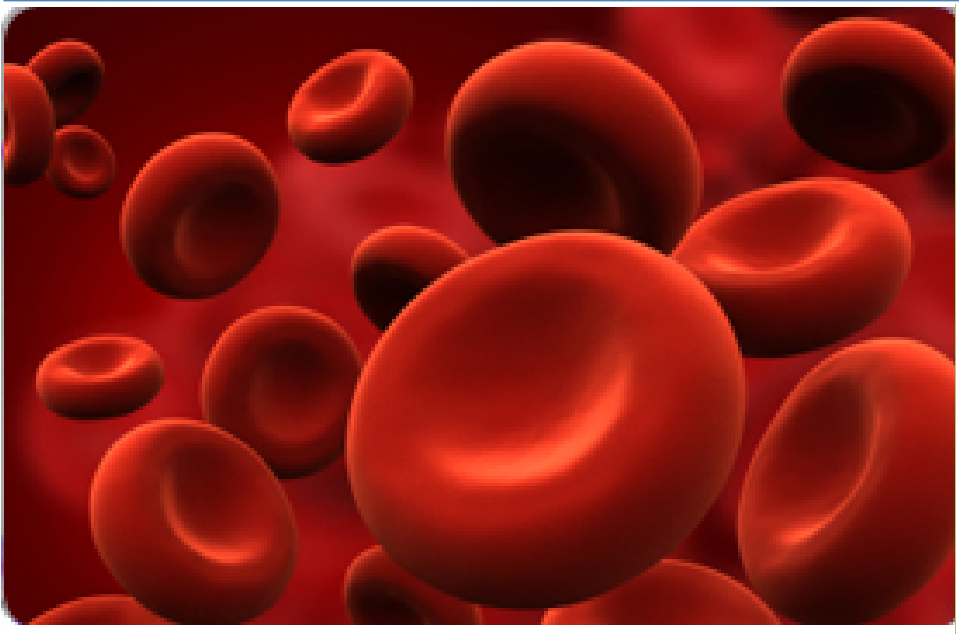
Medical Committee
The University of Jordan

Hematology

Physiology



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25/9/2014

Slides #2

Dr.Saleem Khresha

Table 27–1. Normal values for the cellular elements in human blood.

Cell	Cells/μL (average)	Approximate Normal Range	Percentage of Total White Cells
Total WBC	9000	4000–11,000	...
Granulocytes			
Neutrophils	5400	3000–6000	50–70
Eosinophils	275	150–300	1–4
Basophils	35	0–100	0.4
Lymphocytes	2750	1500–4000	20–40
Monocytes	540	300–600	2–8

Table 19.3 Summary of Formed Elements in Blood

Name and Appearance	Number	Characterictics*	Functions
Red blood cells (RBCs) or erythrocytes 	4.8 million/μL in females; 5.4 million/μL in males.	7–8 μm diameter, biconcave discs, without a nucleus; live for about 120 days.	Hemoglobin within RBCs transports most of the oxygen and part of the carbon dioxide in the blood.
White blood cells (WBCs) or leukocytes	5000–10,000/μL.	Most live for a few hours to a few days.†	Combat pathogens and other foreign substances that enter the body.
Granular leukocytes			
Neutrophils 	60–70% of all WBCs.	10–12 μm diameter; nucleus has 2–5 lobes connected by thin strands of chromatin; cytoplasm has very fine, pale lilac granules.	Phagocytosis. Destruction of bacteria with lysozyme, defensins, and strong oxidants, such as superoxide anion, hydrogen peroxide, and hypochlorite anion.
Eosinophils 	2–4% of all WBCs.	10–12 μm diameter; nucleus has 2 or 3 lobes; large, red-orange granules fill the cytoplasm.	Combat the effects of histamine in allergic reactions, phagocytize antigen–antibody complexes, and destroy certain parasitic worms.
Basophils 	0.5–1% of all WBCs.	8–10 μm diameter; nucleus has 2 lobes; large cytoplasmic granules appear deep blue-purple.	Liberate heparin, histamine, and serotonin in allergic reactions that intensify the overall inflammatory response.
Agranular leukocytes			
Lymphocytes (T cells, B cells, and natural killer cells) 	20–25% of all WBCs.	Small lymphocytes are 6–9 μm in diameter; large lymphocytes are 10–14 μm in diameter; nucleus is round or slightly indented; cytoplasm forms a rim around the nucleus that looks sky blue; the larger the cell, the more cytoplasm is visible.	Mediate immune responses, including antigen–antibody reactions. B cells develop into plasma cells, which secrete antibodies. T cells attack invading viruses, cancer cells, and transplanted tissue cells. Natural killer cells attack a wide variety of infectious microbes and certain spontaneously arising tumor cells.
Monocytes 	3–8% of all WBCs.	12–20 μm diameter; nucleus is kidney shaped or horseshoe shaped; cytoplasm is blue-gray and has foamy appearance.	Phagocytosis (after transforming into fixed or wandering macrophages).
Platelets (thrombocytes) 	150,000–400,000/μL.	2–4 μm diameter cell fragments that live for 5–9 days; contain many vesicles but no nucleus.	Form platelet plug in hemostasis; release chemicals that promote vascular spasm and blood clotting.

Table 12.7 Types of white cell in Romanowsky-stained blood films.

WHITE-CELL TYPES

Cell	Diameter (μm)	Nucleus	Cytoplasm	% of total (adults)
Neutrophil	12–15	2–5 lobes	Pink, granular; fine purple granules	40–75
Lymphocyte	6–8 (small) 12–16 (large)	Round; heavy chromatin	Thin rim, pale blue; occasional granule	20–45
Monocyte	12–20	Large, irregular; fine chromatin	Bulky, pale blue-grey	2–10
Eosinophil	12–15	Two lobes	Many large, oval, orange-red granules	1–6
Basophil	12–15	Large; irregular lobes	Few dark-blue granules; often overlie nucleus	<1

Table 9.4 LEUKOCYTE GRANULE CONTENTS

Cells	Specific Granules	Azurophilic Granules
Neutrophils	Alkaline phosphatase	Acid phosphatase
	Collagenase	α-Mannosidase
	Lactoferrin	Arylsulfatase
	Lysozyme	β-Galactosidase
		β-Glucuronidase
		Cathepsin
		5′ Nucleotidase
		Elastase
		Collagenase
		Myeloperoxidase
		Lysozyme
		Acidic mucosubstances
		Cationic antibacterial proteins
Eosinophils	Acid phosphatase	
	Arylsulfatase	
	β-Glucuronidase	
	Cathepsin	
	Phospholipase	
	RNAse	
	Eosinophilic peroxidase	
	Major basic protein	
Basophils	Eosinophilic chemotactic factor	
	Heparin	
	Histamine	
	Peroxidase	

Table 1.3 Ninety five per cent confidence limits for the concentrations of various types of circulating blood cell in adult Caucasians and their life-span in the blood.

Cell type	Normal range (95% confidence limits)	Life-span in blood
Red cells	Males 4.4–5.8 × 10^{12}/litre Females 4.1–5.2 × 10^{12}/litre	110–120 days
White cells (leucocytes)	4.0–11.0 × 10^{9}/litre	
Neutrophil granulocytes	1.5–7.5 × 10^{9}/litre	$t_{1/2}$ approx. 7 hours
Eosinophil granulocytes	0.02–0.60 × 10^{9}/litre	$t_{1/2}$ approx. 6 hours
Basophil granulocytes	0.01–0.15 × 10^{9}/litre	
Monocytes	0.2–0.8 × 10^{9}/litre	$t_{1/2}$ approx. 70 hours
Lymphocytes	1.2–3.5 × 10^{9}/litre	
Platelets	160–450 × 10^{9}/litre	9–12 days

The bone marrow is actually one of the largest organs in the body, approaching the size and weight of the liver. It is also one of the most active. Normally, 75% of the cells in the marrow belong to the white blood cell-producing myeloid series and only 25% are maturing red cells, even though there are over 500 times as many red cells in the circulation as there are white cells. This difference in the marrow reflects the fact that the average life span of white cells is short, whereas that of red cells is long.

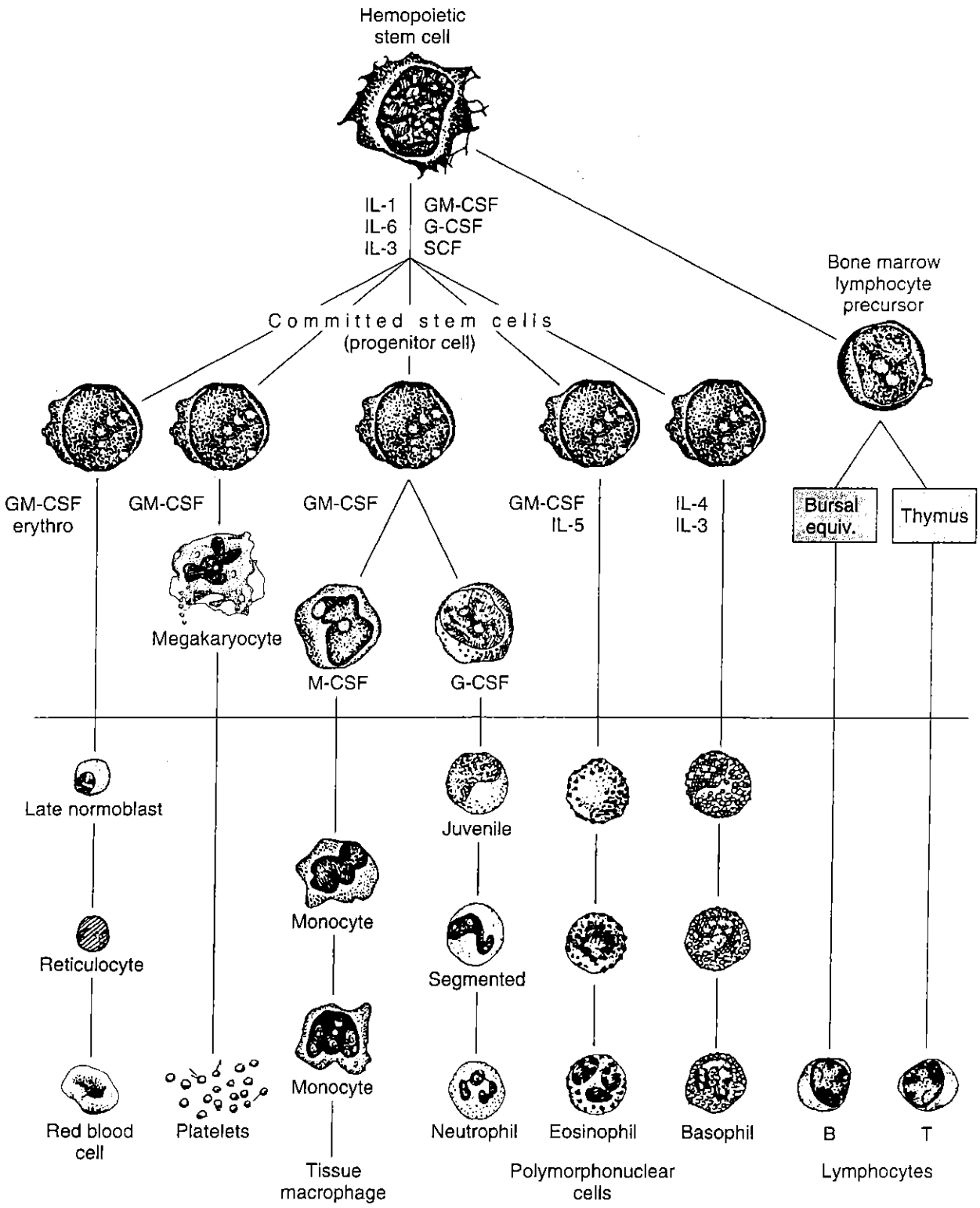

Figure 27–2 Development of various formed elements of the blood from bone marrow cells. Cells below the horizontal line are found in normal peripheral blood. The principal sites of action of erythropoietin (erythro) and the various colony-stimulating factors (CSF) that stimulate the differentiation of the components are indicated. G, granulocyte; M, macrophage; IL, interleukin; see Tables 27–2 and 27–3.

Interleukins IL-1 and IL-6 followed by IL-3 act in sequence to convert pluripotential uncommitted stem cells to committed progenitor cel

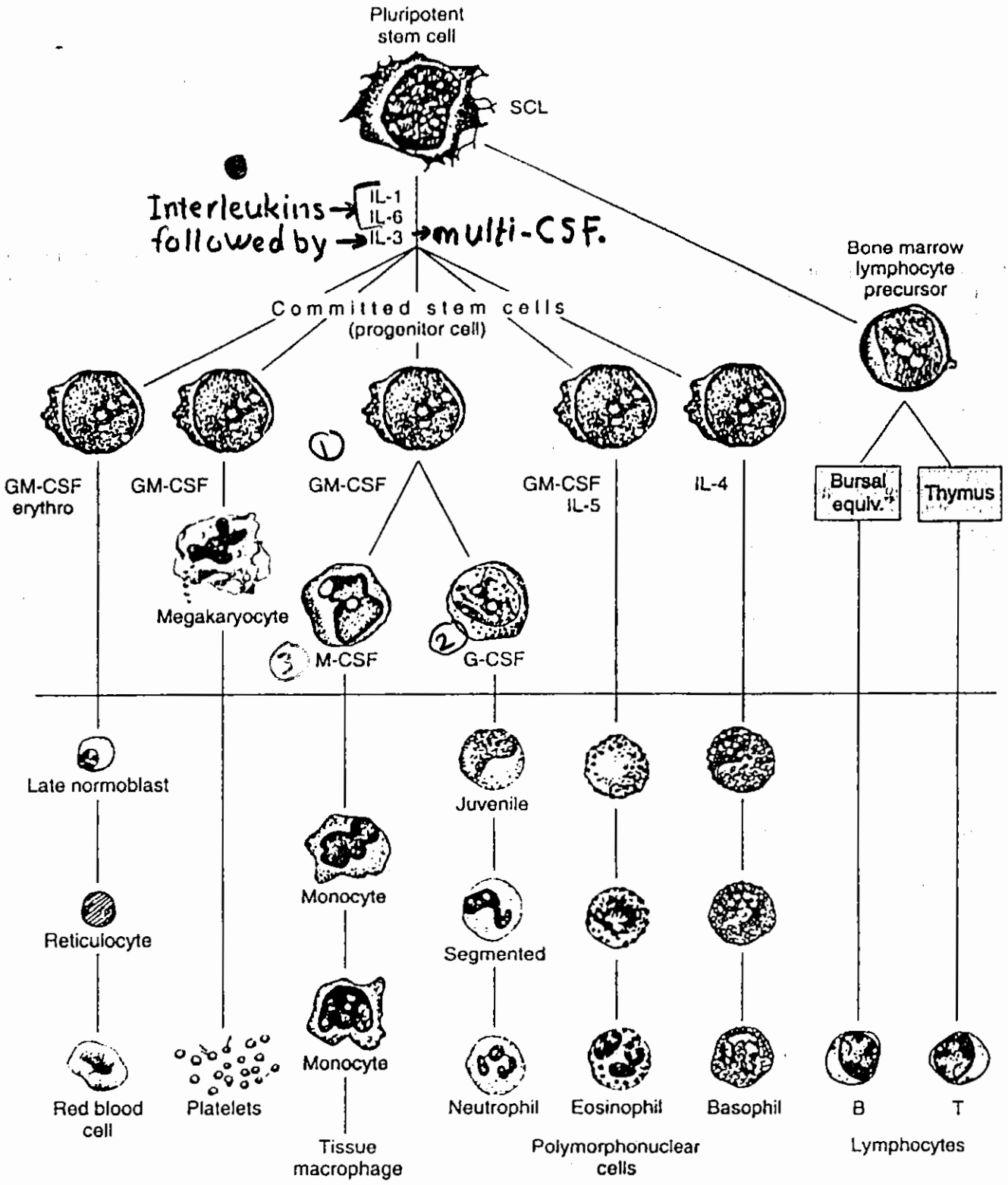

Figure 27–2. Development of various formed elements of the blood from bone marrow cells. Cells below the horizontal line are found in normal peripheral blood. The principal sites of action of erythropoietin (erythro) and the various colony-stimulating factors (CSF) that stimulate the differentiation of the components are indicated. G, granulocyte; M, macrophage; IL, interleukin; see Tables 27–2 and 27–4.

The factors stimulating the production of committed stem cells include 1 + 2 + 3 ↑. These factors are called colony-stim factors (CSFs), because they cause appropriate single stem cells to proliferate forming colonies in culture medium. Each of the CSFs a predominant action, but all the CSFs and interleukins

Table 27–2. Principal cytokines.

Cytokine	Cell Lines Stimulated	Cytokine Source
IL-1	Erythrocyte Granulocyte Megakaryocyte Monocyte	Multiple cell types
IL-3	Erythrocyte Granulocyte Megakaryocyte Monocyte	T lymphocytes
IL-4	Basophil	T lymphocytes
IL-5	Eosinophil	T lymphocytes
IL-6	Erythrocyte Granulocyte Megakaryocyte Monocyte	Endothelial cells Fibroblasts Macrophages
IL-11	Erythrocyte Granulocyte Megakaryocyte	Fibroblasts Osteoblasts
Erythropoietin	Erythrocyte	Kidney Kupffer cells of liver
SCF	Erythrocyte Granulocyte Megakaryocyte Monocyte	Multiple cell types
G-CSF	Granulocyte	Endothelial cells Fibroblasts Monocytes
GM-CSF	Erythrocyte Granulocyte Megakaryocyte	Endothelial cells Fibroblasts Monocytes T lymphocytes
M-CSF	Monocyte	Endothelial cells Fibroblasts Monocytes
Thrombopoietin	Megakaryocyte	Liver, kidney

Key: IL = interleukin; CSF = colony stimulating factor; G = granulocyte; M = macrophage; SCF = stem cell factor

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actin in the neutrophils does not polymerize normally, and the neutrophils move slowly. In another, there is a congenital deficiency of leukocyte integrins. In a more serious disease (chronic granulomatous disease), there is a failure to generate O_2^- in both the neutrophils and monocytes and consequent inability to kill many phagocytosed bacteria. In severe congenital glucose 6-phosphate dehydrogenase deficiency, there are multiple infections because of failure to generate the NADPH necessary for O_2^- production. In congenital myeloperoxidase deficiency, microbial killing power is reduced because hypohalite ions are not formed.

Lymphocytes

Lymphocytes are key elements in the production of immunity (see below). After birth, some lymphocytes are formed in the bone marrow. However, most are formed in the lymph nodes (Figure 27–4), thymus, and spleen from precursor cells that originally came from the bone marrow and were processed in the thymus or bursal equivalent (see below). Lymphocytes enter the bloodstream for the most part via the lymphatics. At any given time, only about 2% of the body lymphocytes are in the peripheral blood. Most of the rest are in the lymphoid organs. It has been calculated that in humans, 3.5×10^{10} lymphocytes per day enter the circulation via the thoracic duct alone; however, this count includes cells that reenter the lymphatics and thus traverse the thoracic duct more than once. The effects of adrenocortical hormones on the lymphoid organs, the circulating lymphocytes, and the granulocytes are discussed in Chapter 20.

IMMUNITY

Overview

Insects and other invertebrates have **innate immunity.** The key to this system is receptors that bind sequences of sugars, fats, or amino acids in common bacteria and activate various defense mechanisms. The receptors are coded in the germ line, and their fundamental structure is not modified by exposure to antigen. The activated

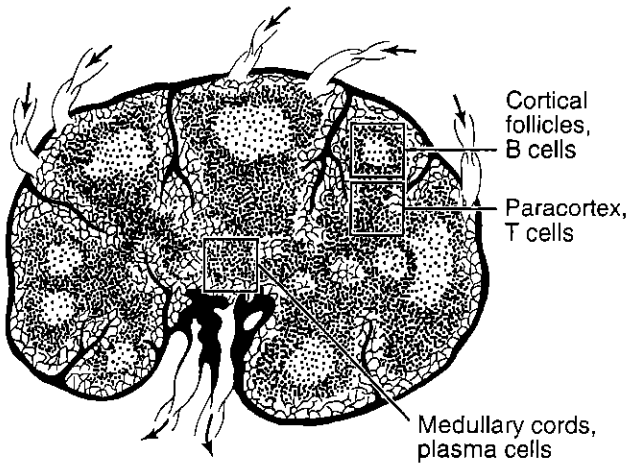


Figure 27–4 Anatomy of a normal lymph node. (After Chandrasoma. Reproduced, with permission, from McPhee SJ, Lingappa VR, Ganong WF [editors]: *Pathophysiology of Disease,* 4th ed. McGraw-Hill, 2003.)

Functions of the Leucocytes:-

All leucocytes possess, to some degree, four basic properties that relate to their functions in the body.

They are able to pass through the walls of capillaries, to enter the tissue spaces in accordance with the local needs. This process (I) is known as *diapedesis*. Once within the tissue spaces, the leukocytes (particularly the polymorphonucleocytes) have the ability to move through the tissues by an ameboid motion (II) at speeds of up to 40 μm min^{-1}. Furthermore, they seem to be attracted by certain chemical substances released by bacteria or by inflamed tissues (*chemotaxis*) (III).

Phagocytosis (IV): The ability to engulf and digest or kill bacteria and products of cell death.

One of the remarkable features of neutrophils is their fine capacity to distinguish foreign cells like bacteria from homologous body cells and aged or damaged cells from fresh ones. This is due to the presence in plasma of certain substances (**opsonins**), such as **γ-globulins** (especially immunoglobulin G (IgG)) and **complement C4**, which coat bacteria and ageing cells, thereby making them 'palatable' to neutrophils. To opsonize means to prepare for eating. An opsonin is an agent in plasma which acts on foreign particles to increase their palatability to phagocytes.

Table 1.4 Main functions of blood cells.

Type of cell	Main functions
Red blood cells (erythrocytes)	Transport O_2 from lungs to tissues; transport CO_2 from tissues to lungs
Granulocytes	
Neutrophil	Chemotaxis, phagocytosis, killing of phagocytosed bacteria
Eosinophil	All neutrophil functions listed above, effector cells for antibody-dependent damage to metazoal parasites, regulate immediate type hypersensitivity reactions (inactivate histamine and slow-reacting substance of anaphylaxis released by basophils and mast cells)
Basophil	Mediate immediate-type hypersensitivity (IgE-coated basophils react with specific antigen and release histamine and slow reacting substance of anaphylaxis), modulate inflammatory responses by releasing heparin and proteases
Monocytes	Chemotaxis, phagocytosis, killing of some microorganisms, become macrophages
Platelets	Adhere to subendothelial connective tissue, participate in blood clotting (see p. 162)
Lymphocytes	Involved in immune responses

Table 1.2 Morphology of normal white cells in Romanowsky-stained smears of peripheral blood.

Cell type	Cell size (μm)	Colour	Cytoplasm: Ratio of cytoplasmic volume to nuclear volume	Cytoplasm: Granules	Nucleus
Neutrophil granulocytes	9–15	Slightly pink	High	Numerous, very fine, faint purple	Usually 2–5 segments
Eosinophil granulocytes	12–17	Pale blue	High	Many, large and rounded, reddish-orange	Usually two segments
Basophil granulocytes	10–14		High	Several, large and rounded, dark purplish-black	Usually two segments, granules overlie nucleus
Monocytes	15–30	Pale greyish-blue, cytoplasmic vacuoles may be seen	Moderately high or high	Variable number, fine, purplish-red	Various shapes (rounded, C- or U-shaped, lobulated), skein-like or lacy chromatin
Lymphocytes	7–12 (small lymphocytes); 12–16 (large lymphocytes)	Pale blue	Low or very low	Few, fine, purplish-red	Rounded with large clumps of condensed chromatin

Table 19.2 Significance of High and Low White Blood Cell Counts

WBC Type	High Count May Indicate	Low Count May Indicate
Neutrophils	Bacterial infection, burns, stress, inflammation.	Radiation exposure, drug toxicity, vitamin B_{12} deficiency, and systemic lupus erythematosus (SLE).
Lymphocytes	Viral infections, some leukemias.	Prolonged illness, immunosuppression, and treatment with cortisol.
Monocytes	Viral or fungal infections, tuberculosis, some leukemias, other chronic diseases.	Bone marrow suppression, treatment with cortisol.
Eosinophils	Allergic reactions, parasitic infections, autoimmune diseases.	Drug toxicity, stress.
Basophils	Allergic reactions, leukemias, cancers, hypothyroidism.	Pregnancy, ovulation, stress, and hyperthyroidism.

Types of Leukemia.

Leukemias are divided into two general types:

1- lymphocytic leukemias.
2. myelocytic leukemias.

* The leukemia cells are bizarre & undifferentiated & not identical with any of the normal white blood cells.

* Usually the more undifferentiated the cells the more acute is the leukemia.

* But with some of the more differentiated cells, the process can be quite chronic, sometimes developing slowly over a period of 10-20 years.

* Leukemic cells, especially the very undifferentiated cells, are usually nonfunctional.

Effects of Leukemia on the Body:

1. The first effect of leukemia is metastatic growth of leukemic cells in abnormal areas of the body.

2. The leukemic cells of the bone marrow invade the surrounding bone.

3. Almost all leukemias spread to the spleen, the lymph nodes, the liver & vascular regions.

4. In each of these areas the rapidly growing cells invade the surrounding tissues, utilizing the metabolic elements of these tissues & consequently ~~casing~~ causing tissue destruction.

5. Very common effects in leukemia are the development of infections, severe anemia & bleeding tendency caused by thrombocytopenia (lack of platelets).

6. The most important effect of leukeima on the body is the excessive use of metabolic substrates by the growing cancerous cells.

7. Tremendous demands are made on the body for foodstuffs, especially the amino acids & vitamins. Consequently, the energy of the patient is greatly depleted, rapid deterioration of the normal protein tissues of the body.

8. Obviously, after metabolic starvation has continues long enough, this alone is sufficient to cause death.

Leucocytes

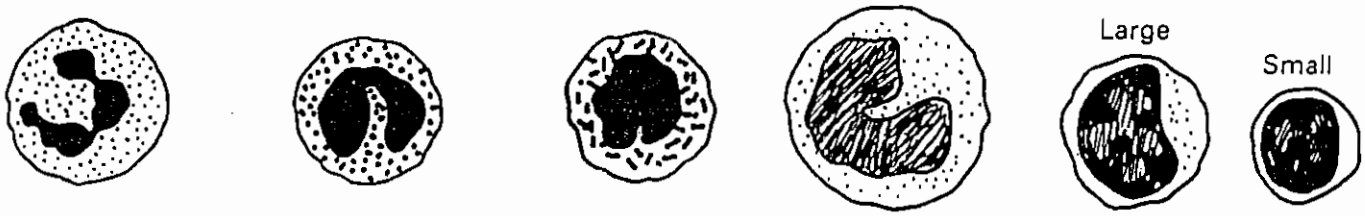
Classification

The blood leucocytes (white blood cells) are a heterogeneous population of nucleated cells lacking haemoglobin. There are five distinct morphological types classified into two groups on the basis of the presence or absence of granules in their cytoplasm:

1 **Granulocytes** (with cytoplasmic granules): these are the neutrophils, eosinophils and basophils.

2 **Agranulocytes** (without cytoplasmic granules): these are the monocytes and lymphoctyes.

Figure 2.5 gives the dimensions and morphological characteristics of the leucocytes.



Neutrophil 40–60%	Eosinophil 0.5–1%	Basophil 0.5–1%	Monocyte 6–10%	Lymphocyte 20–40%
Morphological features: Diameter 10–16μm	Diameter 12–18μm	Diameter 10–14μm	Diameter 15–20μm	Diameter 5–8μm (small lymphocyte) 9–15μg (medium and large lymphocyte)
Nucleus: Lobulated (2–5 lobes) connected by chromatin strands. Nucleus is made of dense masses which take the purple stain	Made usually of 2 lobes – stains less deeply than neutrophil	Rarely segmented and its margins are usually obscured by the overlying cytoplasmic granules	Usually kidney shaped. Nuclear chromatin made of interwoven threads which are without compact blocks. Stains faintly	Rounded or slightly indented. Nuclear chromatin is clumped in the form of dark masses
Cytoplasm: Contains fine granules which stain purplish	Contains the characteristic large spherical bright red granules	Contains large coarse rounded or oval dark deeply staining granules which overlie the nucleus	Grey-blue giving a ground glass appearance with fine reddish azurphilic granules	Large lymphocyte has abundant cytoplasm which usually takes pale blue stain and may contain fine reddish granules Small lymphocyte has a very scanty cytoplasm forming a small rim around the nucleus

Fig. 2.5 The shapes, dimensions and special morphological features of the various types of leucocytes.

Total leucocyte count

Although it is usually quoted in textbooks that the total leucocyte count is 4000 to 10 000 cells per cubic millimetre of blood, it should be emphasized that this range applies more to Europeans than to residents of hot tropical countries. It is not uncommon to find a total leucocyte count among healthy students and blood donors in these geographical locations of between 2000 and 4000 cells/mm^3. Because there is a relatively low count of neutrophils, this is called *neutropenia*.

Differential white cell counts

The normal proportions of white blood cells are as follows:

Neutrophils	60–70%
Lymphocytes	20–30%
Monocytes	2–8%
Eosinophils	2–4%
Basophils	0–2%

Leucocytosis and leucopenia

An increase in the total leucocyte count above the normal

is called leucocytosis. This may occur in health (physiological leucocytosis) or disease.

Physiological leucocytosis may occur under several conditions:

1 Diurnal variation: leucocyte counts are lowest in the morning and increase to a maximum in the afternoon.

2 After a protein meal.

3 Following physical exercise.

4 Stimulation by stress or an injection of adrenaline (epinephrine).

Disease states which commonly cause leucocytosis are bacterial infections (pyogenic infections), e.g. tonsillitis, infected wounds or inflamed appendix. In these conditions, measurement of the total leucocyte count is essential for diagnosing the existence of the infection. The differential white cell count is also useful. In general, acute bacterial infections cause an increase in the neutrophil count, while chronic and viral infections are associated with an increased lymphocyte count.

Leucopenia is a decrease in the total leucocyte count below the normal. It is often seen in conditions of malnutrition and is also an important feature of typhoid fever. Some drugs may depress the bone marrow and therefore result in leucopenia and, in particular, a decrease in the granulocyte count (agranulocytosis). Leucopenia can also be caused by a deficiency of vitamin B_{12} or folic acid.

Lymphocytes in the bloodstream

Lymphocytes enter the peripheral blood either directly, by passing through the walls of blood-vessels in the various lymphopoietic organs, or indirectly, by entering the lymph stream and eventually reaching the bloodstream through the thoracic duct and other lymph ducts in the neck.

Classification

When seen under an ordinary light microscope, blood lymphocytes can be divided into **small** (5–8 μm diameter) and **large lymphocytes** (8–15 μm diameter). The majority of blood lymphocytes are of the small type.

Functions

Lymphocytes are the central cells in immunity. On the

basis of this function, lymphocytes are divided into two types:

1 *Thymus-dependent lymphocytes (T cells)* are so called because they originate in the thymus or bone marrow and migrate to the thymus where they mature and are reprogrammed to recognize foreign antigens. They have a lifespan of 100–300 days or even more (hence the name long-lived lymphocytes). This long lifespan is closely related to their property of constant movement from blood to tissues to lymph to blood again (*recirculation of lymphocytes*).

T lymphocytes are the principal mediators of **cellular immune responses**, such as rejection of tissue graft, e.g. kidney transplant, and delayed hypersensitivity reactions. They also play a minor role in the synthesis of immunoglobulins (antibodies).

2 *Thymus-independent lymphocytes (B cells)*. In humans, the B cells develop in the bone marrow, the germinal centres of lymph nodes and the red pulp of the spleen. Their lifespan is 2–7 days (hence the name short-lived lymphocytes). They have been called B cells because they are known as bursa cells. When the B cells are properly stimulated by an antigen, they develop successively into large lymphocytes and, lastly, plasma cells. The plasma cells are lymphoid cells which are capable of producing **antibodies**. Thus, the B lymphocytes are the principal mediators of the **humoral immune response**.

Formation of leucocytes (leucopoiesis)

Sites of formation

1 **Granulocytes**: bone marrow.

2 **Lymphocytes**: bone marrow, thymus, lymph nodes and other collections of lymphoid tissues, e.g. wall of the intestine.

3 **Monocytes**: bone marrow.

Formation of granulocytes (granulopoiesis)

The life history of the granulocytes begins in the bone marrow, where there is progressive division and maturation from the earliest cell, the stem cell, successively through the cell types myeloblast, promyelocyte, myelocyte, metamyelocyte, band neutrophil and segmented neutrophil. The myeloblasts, promyelocytes and myelocytes are capable of mitotic division and cell replication; hence, these are collectively called the **proliferating granulocyte pool**. From the metamyelocyte stage onwards, no cell division occurs and therefore the metamyelocytes, band neutrophils and segmented neutrophils are together referred to as the **maturation pool**. Maturation takes the form of biochemical and morphological changes in both the nucleus and the cytoplasm. The nucleus becomes condensed and broken up into lobes. In addition, fine neutrophilic granules appear in the cytoplasm. The maturation pool is sometimes called the **marrow granulocyte reserve**, as it is believed to be the main source of extra neutrophils which enter the bloodstream in acute infections and other pathological states. The mature neutrophils, once released into the bloodstream, stay there for about 7–10 hours before they migrate to the tissues, where they function as mobile phagocytes.

Haemopoietic growth factors

The formation of all blood cells is sustained throughout life by a group of glycoprotein growth factors, the *haemopoietic growth factors* (collectively called *colony-stimulating factors*, **CSF**). The first to be discovered was erythropoietin. Others which control the production of white blood cells include: multipotential CSF, granulocyte–macrophage CSF and granulocyte CSF. Recently, these growth factors have found important clinical uses by stimulating the bone marrow activity in disease conditions such as bone marrow failure, haematological malignancies and infectious diseases.

Neutrophils in the bloodstream

Mature neutrophils leave the bone marrow to enter the blood. Some of them join the blood circulation—the so-called **circulating granulocyte pool**. These are the

cells available for blood sampling and counting. Others are deposited along the walls of the small vessels (**marginal granulocyte pool**), where they are in a state of rapid and continuous exchange with the circulating cells, and from this site they can be mobilized by exercise or by an adrenaline (epinephrine) injection. The entry of these cells into the circulating pool accounts for the increased white cell count (leucocytosis) that accompanies exercise and other stressful situations.

Functions of leucocytes

The general function of leucocytes is defence against infection. However, the different types of leucocytes contribute to a different extent towards this general function.

Functions of neutrophils

The neutrophils are also called **polymorphonuclear leucocytes** because the nucleus is formed of two to five lobes. This cell is the most important cell in the cellular defences of the body against infection. To achieve this goal, neutrophils execute several integrated functions: (i) the neutrophils must reach the site of infection (**chemotaxis**); (ii) they must ingest the foreign organism (**phagocytosis**); and (iii) they must kill or inhibit the multiplication of the microorganism (**microbial killing**).

Chemotaxis

The neutrophils are actively motile cells; they can move more rapidly than any other cell in the body. Their movement is directed towards bacteria in a purposeful manner, being attracted to bacteria or the site of infection or inflammation by a variety of chemotactic substances, e.g. products of certain bacteria, damaged leucocytes or other tissue components. The property of directed movement of the neutrophils is named **chemotaxis**. It accounts for the accumulation of neutrophils at sites where they are needed, e.g. infected wounds. Impaired chemotaxis can lead to increased susceptibility to infectious diseases, especially in children.

When neutrophils approach the infected site, they lie along the walls of the closest capillaries—a process called **margination**. Then individual neutrophils squeeze themselves between endothelial cells and gradually move out from the capillary—a process called **diapedesis**. Since neutrophils are motile cells, they move towards the bacteria.

Phagocytosis

Phagocytosis is the process whereby a cell eats particulate matter (Fig. 2.6).

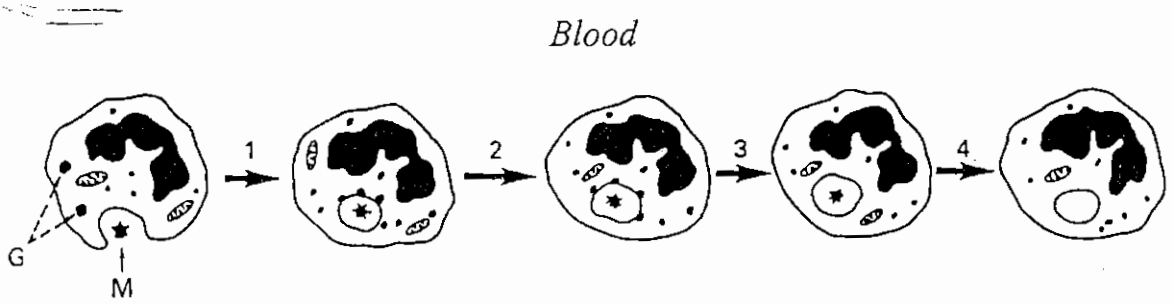


Fig. 2.6 Schematic diagram of the process of phagocytosis by a neutrophil. An ops onized microbe (M) after being recognized by the neutrophil is contained in an invagination of the neutrophil membrane. T hereafter, the particle is enclosed in a phagocytic vaaiole. Son of the neutrophil granules (G) stick to the wall of the vacuole and th en release their bactericidal substances, which induce klling and ultimate digestion of the microbe.

One of the remarkable features of neutrophils is their fine capacity to distinguish foreign cells like bacteria from homologous body cells and aged or damaged cells from fresh ones. This is due to the presence in plasma of certain substances (**opsonins**), such as **γ-globulins** (especially immunoglobulin G (IgG)) and **complement C4**, which coat bacteria and ageing cells, thereby making them 'palatable' to neutrophils. To opsonize means to prepare for eating. An opsonin is an agent in plasma which acts on foreign particles to increase their palatability to phagocytes.

Recognition is followed by close adhesion between the outer membrane of the neutrophil and the bacterium. This is followed by invasion of the neutrophil membrane and complete encirclement of the bacterium by pseudopodia. The pseudopodia fuse to enclose the bacterium in a phagocytic vacuole.

Microbial killing

Following the ingestion (phagocytosis) of the bacterium, the following sequence of events take place:

1 The fusion of the neutrophilic granules with the phagocytic vacuole.

2 Discharge of antimicrobial agents from the granules into the vacuole. These agents include lysozymes, myeloperoxidase and lactoferrin, which are capable of destroying a wide range of bacteria.

3 Killing and digestion of the ingested organism.

Functions of eosinophils (acidophils)

The eosinophils are characterized by the presence of coarse, bright red granules in their cytoplasm. These granules contain an arginine-rich basic protein which attracts red acidic dyes like eosin. The eosinophil nucleus is often seen as two large lobes. Eosinophil functions are not very different from those of the neutrophil.

Chemotaxis

Unlike neutrophils, eosinophils are attracted more towards

areas of chronic inflammation rather than acute inflammation. **Chemotactic substances** for eosinophils include histamine, antigen–antibody complexes, 5-hydroxytryptamine (5-HT), bradykinin and a specific 'eosinophil chemotactic factor'.

Eosinophils tend to accumulate at the sites of histamine release, as is seen in allergic diseases of the skin or lungs.

Phagocytosis

Eosinophils are capable of ingesting a variety of particles, ranging from bacteria and destroyed cells to antigen–antibody complexes. Phagocytosis involves the same sequence of events as already described for neutrophils. However, antimicrobial activity is considerably less than that of the neutrophil. Eosinophils also release **major basic protein** (MBP) which is highly toxic to larvae of parasites.

Eosinophils and inflammation

In inflamed tissues, eosinophils have been shown to be capable of antagonizing and inactivating histamine and other chemical mediators of inflammation, such as 5-HT and bradykinin. Through this function, the eosinophil helps to limit and circumscribe the inflammatory process.

The eosinophilic response to an inflammatory stimulus is characterized by accumulation of eosinophils in the inflamed tissues, with a simultaneous increase both in the production of eosinophils by the bone marrow and in the number of circulating eosinophils (eosinophilia), on their way from the bone marrow to the inflammatory sites. Chronic eosinophilia occurs in response to complex antigens, as in helminthic (worm) infestations (e.g. hook-worm, ascaris and bilharzia) and in response to allografts (e.g. skin grafts).

The accumulation of eosinophils in inflammatory sites may be inhibited by high doses of corticosteroids, which also depress the chemotactic attraction of eosinophils.

(12) *Eosinophilia*

From the foregoing account we may deduce that eosinophilia occurs in pathological states as a result of an antigen —antibody reaction.

Common causes of eosinophilia include:

1 Parasitic disease, e.g. worm infestations of the gut.

2 Allergic conditions:

(a) Bronchial asthma.

(b) Allergic rhinitis (hay fever).

(c) Drug reactions, e.g. penicillin sensitivity.

3 Tropical eosinophilia, which represents a reaction to the filaria parasite.

4 Dermatological diseases.

Functions of basophils

The distinguishing morphological feature of the basophil is the large blue-black granules which appear to fill the cytoplasm, overlie the nucleus and tend to obscure nuclear configuration. Basophil granules contain abundant acid mucopolysaccharide, which accounts for their strong affinity for basic dyes such as methylene blue. Heparin is one of the important acid mucopolysaccharide constituents; other constituents include histamine, 5-HT and ribonucleic acid (RNA). The basophil is the carrier of **histamine** in the blood and, due to its being rich in both heparin and histamine, it bears a strong resemblance to **tissue mast cells**. The function of basophils is not known with certainty but they may have a role related to their content of the physiologically active substances, such as heparin, histamine and 5-HT. Mast cells and basophils have surface Igt receptors which bind IgE coated antigens, degranulate and release histamine leading to allergic reactions e.g. urticaria.

Monocytes (blood macrophages)

This macrophage has its origin in the bone marrow monoblast and promonocyte. The mature monocyte reaches the bloodstream, where it stays for a variable period of time, ranging from a few hours to 6 days. Then it leaves the circulation for the tissues, where it undergoes transformation to the larger and more effective phagocyte—**tissue macrophage (histiocyte)**.

Functions

The macrophage contributes directly to the body defence systems by phagocytosis and killing of invading bacteria and, indirectly, by interacting and cooperating with lymphoid cells in both the afferent (or recognition of foreign material) and efferent (effector) limbs of the **immune response**. In the afferent limb, macrophages process the antigen and present it to lymphocytes.

Macrophages phagocytose damaged or altered host cells and microscopic debris, which justifies the descriptive name '**tissue scavengers**'.

Lymphocytes

Much of our knowledge about the cellular elements of the blood has been based on the concept that cells may be recognized and classified by morphological criteria. This concept, however, does not hold in relation to recognizing and classifying cells of the lymphoid series. The blood lymphocytes constitute a family of cells of different origins, migration patterns, sizes, staining characteristics, ultrastructure, lifespan and function.

Formation (lymphopoiesis)

Lymphocytes originate from the primitive unipotent stem cell (lymphoid-committed precursor) in the **thymus, lymphoid tissues** and **bone marrow** and then proceed along a known maturation line via the 'lymphocyte production pathway', which includes the following cellular stages:

1 *Lymphoblasts*. Normally these are only seen in lymphopoietic organs and almost never observed in peripheral blood.

2 *Intermediate (transitional) forms* (large blast cells).

3 *Small and large lymphocytes* (blood lymphocytes).

These stages are not unidirectional. The process can, under certain circumstances, go in the reverse direction and small lymphocytes can grow into large lymphocytes and lymphoblasts. Such blastic transformation can be demonstrated *in vitro* by growing small lymphocytes in a suitable culture medium containing a non-specific mitogen, such as *phytohaemagglutinin (PHA)*, or a specific antigen, e.g. *tuberculin*.

PHYSIOLOGY AND FUNCTION OF THE BASOPHIL

The basophil is produced in the bone marrow in a manner similar to that of eosinophils and neutrophils. It exhibits chemotaxis and some phagocytic activity. In contrast to the neutrophil, the basophil has a sluggish motility, during which the nucleus advances and is in a forward position within the cell. In the neutrophil and eosinophil, the cytoplasm advances during locomotion. The basophil generally has a two- or three-lobed nucleus. The granules are water-soluble and most probably contain all of the blood histamine. They are peroxidase-positive and also contain a slow-reacting substance of anaphylaxis, platelet activating factor, kallikrein, and eosinophil chemotactic factor, and large amounts of heparin. The basophil has a secretory function in that it releases its granule contents to the outside of the cell (exocytosis) following exposure to various stimuli. They have also been shown to migrate to areas where foreign protein is present. Little is known of the function of the basophil, but it apparently participates in allergic reactions. The basophils increase in the peripheral blood in chronic myelogenous leukemia, myelofibrosis, and polycythemia vera.

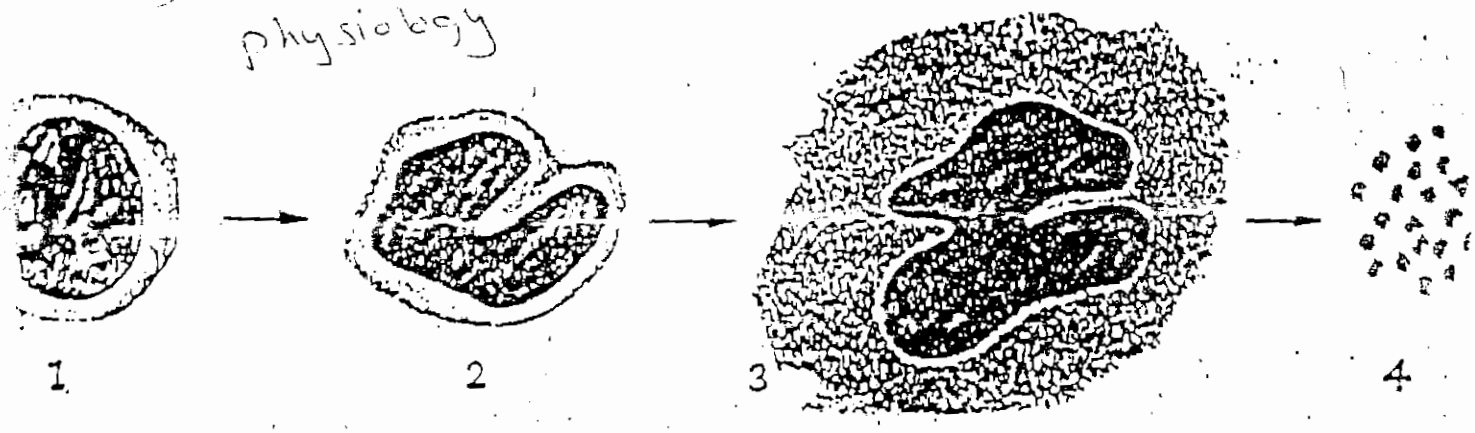
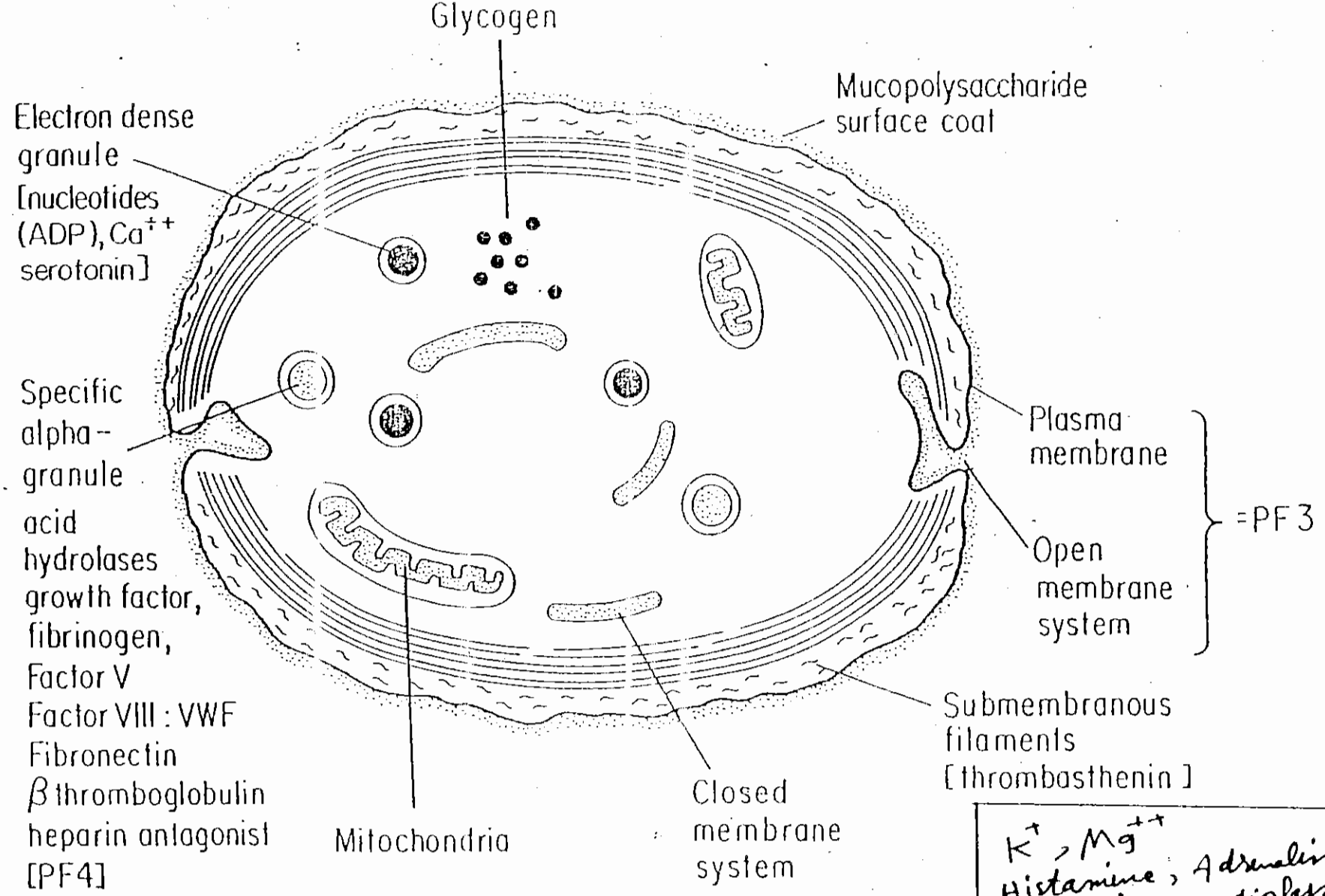


Fig. 2.5.3. Development of platelets — 1, promegakaryoblast 2, megakaryoblast 3, megakaryocyte 4, platelets

Platelets are developed from the giant cells called *'megakaryocytes' in the bone marrow*, whose diameter is usually around 100 μm. A single megakaryocyte can give rise to about 4000 platelets.

Normally, the bone marrow contains only about one day's reserve of platelets. Therefore, human beings are susceptible to develop thrombocytopenia more quickly than granulocytopenia or erythrocytopenia.



K^{+}, Mg^{++}
Histamine, Adrenalin
Albumin, Antiplasmin
Lipoproteins, Prostaglandins
Thromboxanes.

Fig. 11.2 Diagrammatic representation of the ultrastructure of platelets.

HEMOSTASIS

* Physiological hemostatic mechanisms are most effective in dealing with injuries in small vessels (arterioles, capillaries, venules).

* The bleeding from a medium or a large artery is not usually controllable by the body.

* Venous bleeding is less dangerous because veins have low blood pressure.

* If the venous bleeding is into the tissues, the accumulation of blood may increase interstitial pressure enough to eliminate the pressure gradient for continued blood loss.

* Accumulation of blood in the tissues can occur as a result of bleeding from any vessel type and is termed ***hematoma***.

NORMAL HAEMOSTASIS

The cessation of bleeding following trauma to blood vessels results from three processes: (a) the contraction of vessel walls; (b) the formation of a platelet plug at the site of the break in the vessel wall; and (c) the formation of a fibrin clot. The clot forms within and around the platelet aggregates to form a firm haemostatic plug. The relative importance of these three processes probably varies according to the size of the vessels involved. Thus, in bleeding from a minor wound, the formation of a haemostatic plug is probably sufficient in itself, whereas, in larger vessels. contraction of the vessel walls also plays a part in haemostasis. The initial plug is formed almost entirely of platelets but this is too friable on its own and must be stabilized by fibrin formation.

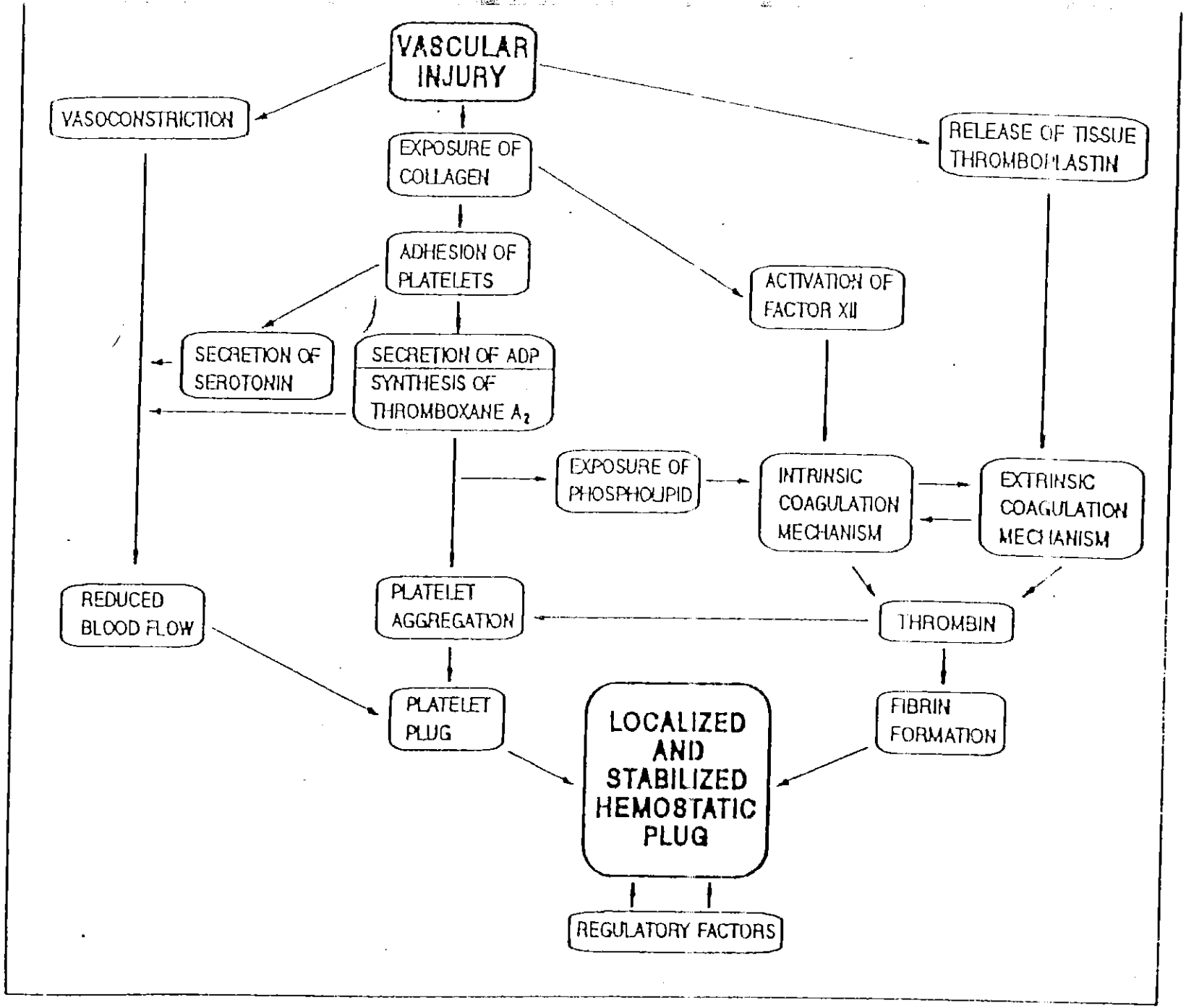
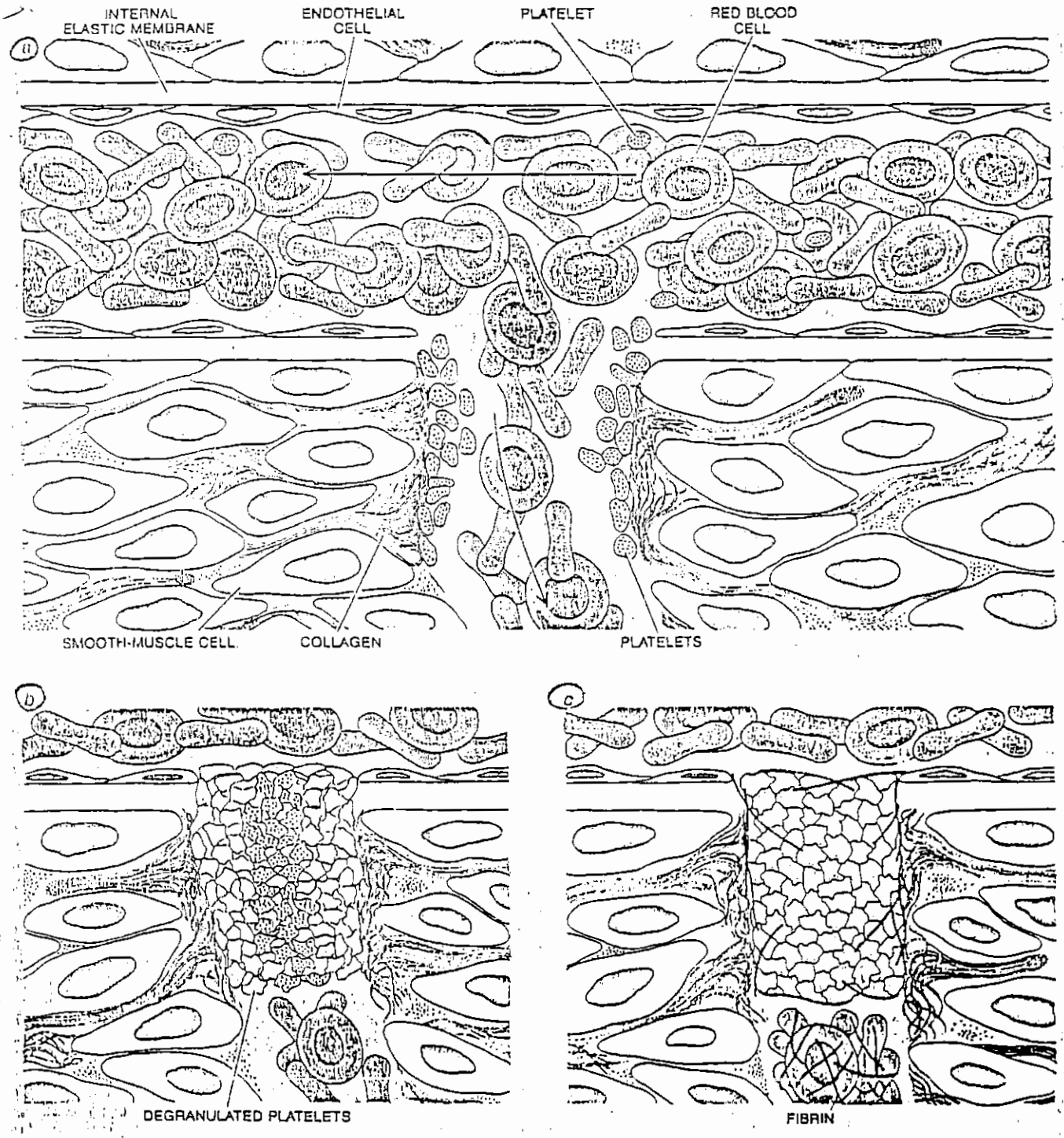


Fig. 25-4. Summary of the integrated hemostatic response to vessel injury. (See text description.)



ROLE OF PLATELETS IN HEMOSTASIS, or the stoppage of bleeding, is diagrammed. As blood begins to flow out through a cut in the vessel wall, platelets adhere to collagen in the wall (*a*). The platelets are thereby stimulated to secrete the contents of their granules, including ADP, and other passing platelets adhere to the first layer, building up a loose plug in the wound channel (*b*). Changes in the platelets and contact of blood with damaged cells convert the plasma protein prothrombin into the enzyme thrombin. The thrombin in turn converts fibrinogen into fibrin strands, which reinforce the platelet plug, and it also causes platelets to pack together more closely (*c*).

Platelet Function

The main function of platelets is the formation of mechanical plugs during the normal haemostatic response to vascular injury.

Central to this function are the platelet reactions of adhesion, release, aggregation & fusion as well as their procoagulant activity.

Platelet Adhesion:

This vital function is dependent upon a part of the factor VIII protein in plasma known as the von Willebrand factor which is part of the main fraction of the factor VIII molecule, factor. VIIIR:AG (factor VIII – related antigen).

Adhesion is also dependent on a platelet surface membrene glycoprotein.

F. VIII: Is a protein produced by
endothelial cell & platelet.

F. VIII. Molecule is made up
of several functional parts.

1. F. VIII:C refers to the coagulant portion
of the molecule & represents the ability
of the molecule to correct coagulation

2. F. VIIIR:AG makes possible platelet
aggregation.

3. F. VIII:VWF that is required for normal platelet
adhesion in hemostasis.

The Release Reaction.

Collagen exposure or thrombin action results in the release of ADP, serotonin, fibrinogen, lysosomal enzymes & heparin neutralising factor (platelet factor 4).

Collagen & thrombin activate platelet prostaglandin synthesis leading to the formation of a labile substance, thromboxane A_2.

This substance not only potentiates platelet aggregation but also has powerful vasoconstrictive activity.

The release reaction is inhibited by substances which increase the level of platelet cyclic AMP.

One such substance is the prostaglandin prostacyclin (PGI_2) which is synthesised by vascular endothelial cells.

It is a potent inhibitor of platelet aggregation & probably prevents their deposition on normal vascular endothelium.

Platelet Aggregation

Released ADP & thromboxane A_2, cause additional platelets to aggregate at the site of vascular injury.

ADP causes platelets to swell & encourages the platelet membranes of adjacent platelets to adhere to each other.

Platelet Procoagulant Activity

After platelet aggregation & release the exposed membrane phospholipid (platelet factor 3) is available for coagulation protein complex formation.

This phospholipid surface forms an ideal template for the crucial concentration & orientation of these proteins for the normal coagulation cascade reactions.

Platelet fusion

High concentrations of ADP, the enzymes released during the release reaction & thrombasthenin contribute to an irreversible fusion of platelets aggregated at the site of vascular injury.

Thrombin also encourages fusion of platelets & fibrin formation reinforces the stability of the evolving platelet plug.

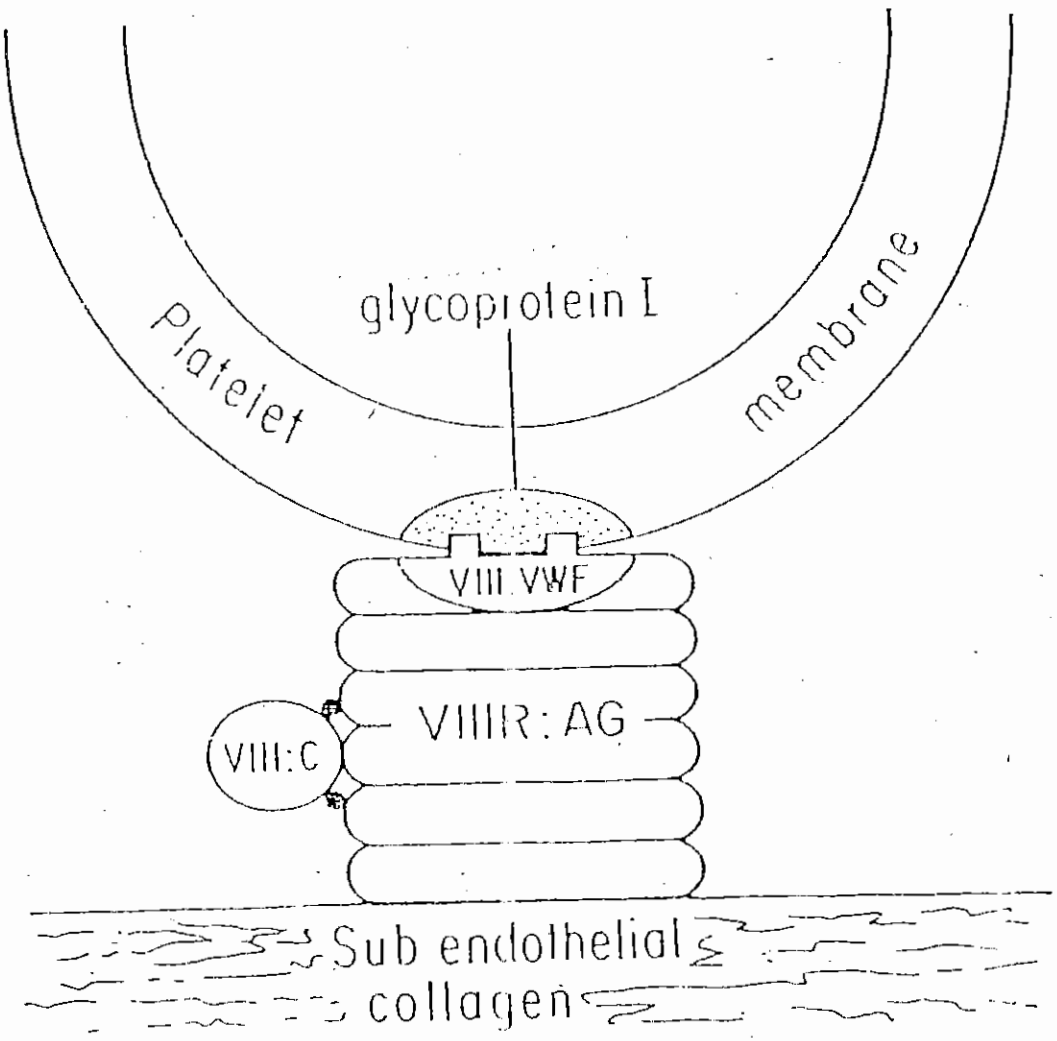
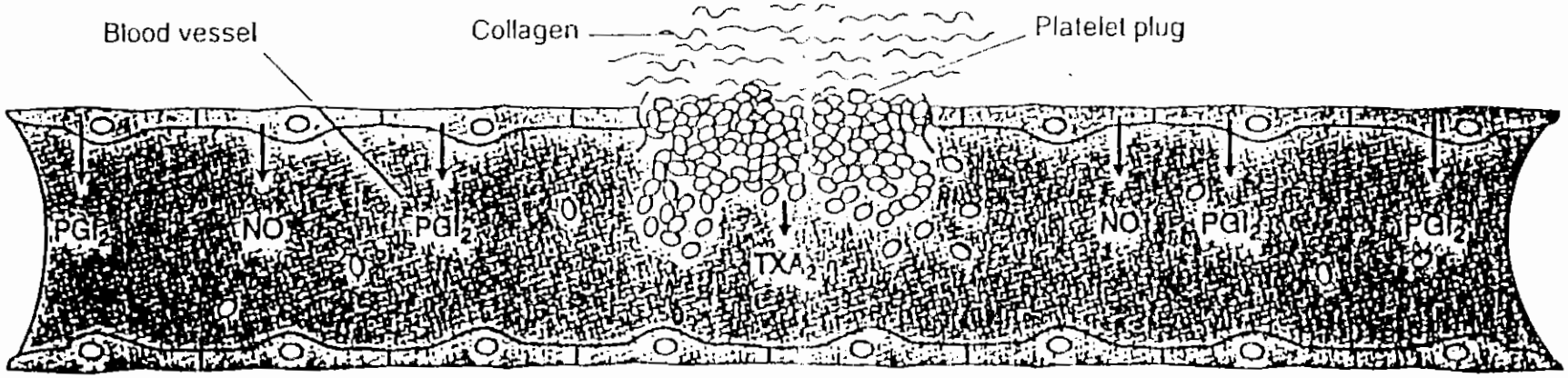


Fig. 11.3 The role of factor VIII:VWF and factor VIIIR:AG in platelet adhesion.

FIGURE 20-21

Platelets produce thromboxane A_2 (TXA_2), whereas normal endothelium adjacent to a platelet plug produces prostaglandin I_2 (PGI_2) from platelet and endothelial-cell arachidonic acid, and this eicosanoid inhibits platelet aggregation. Nitric oxide, NO, also secreted by the endothelial cells, does the same thing as PGI_2. Thus, PGI_2 and NO prevent spread of platelet aggregation from the damaged site.



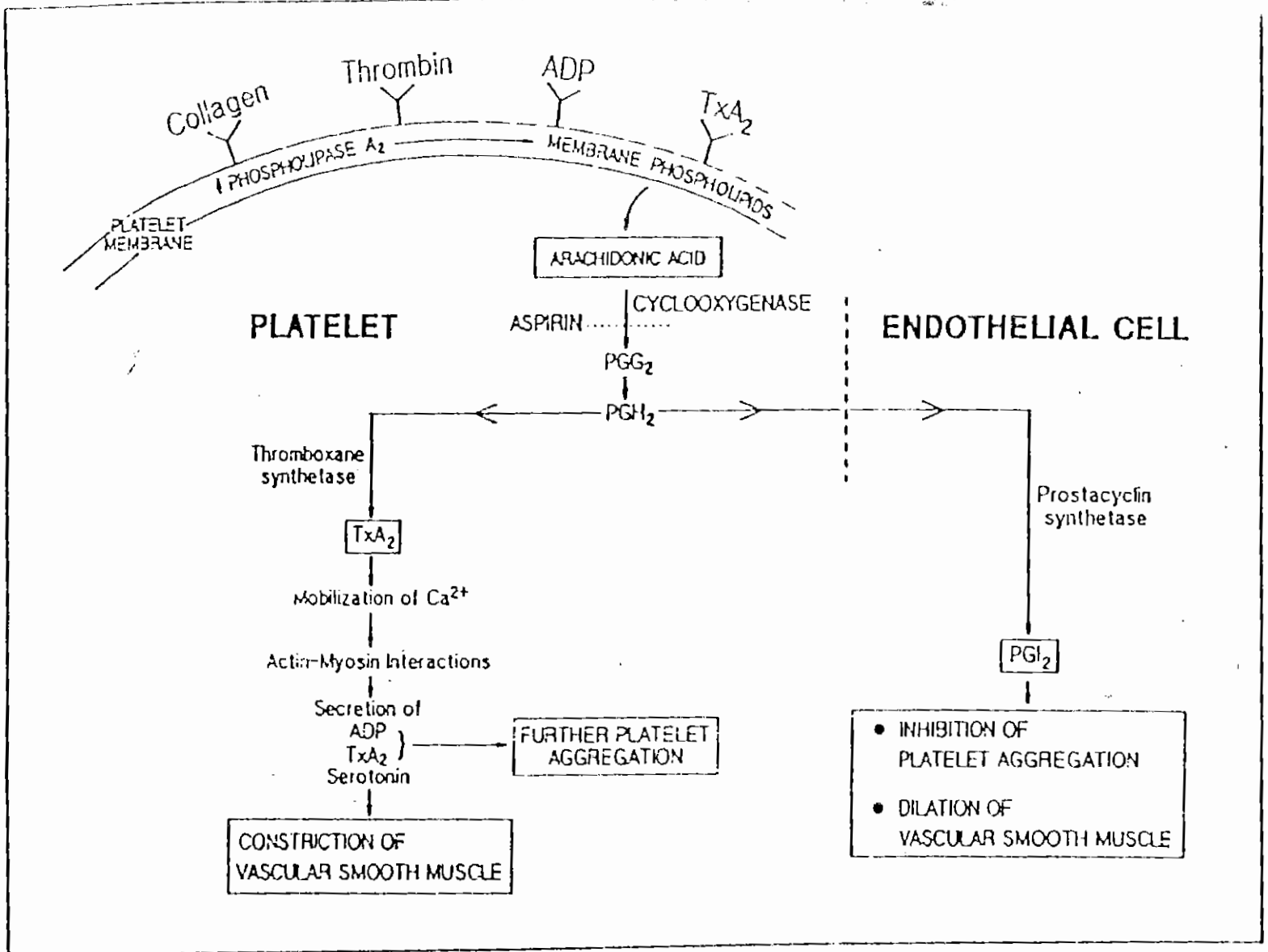


Fig. 24-3. Oxidation of arachidonic acid in the platelet in response to platelet aggregating agents. (*ADP* = adenosine diphosphate; TxA_2 = thromboxane A_2; PGG_2 and PGH_2 = cyclic endoperoxides; PGI_2 = prostacyclin.) Metabolism of arachidonate via the lipoxygenase pathway, leading to the formation of leukotrienes is not shown; its potential role in the platelet aggregation response is not clearly known. To the right of the dashed line is depicted the metabolism of endoperoxides by the endothelial cell.

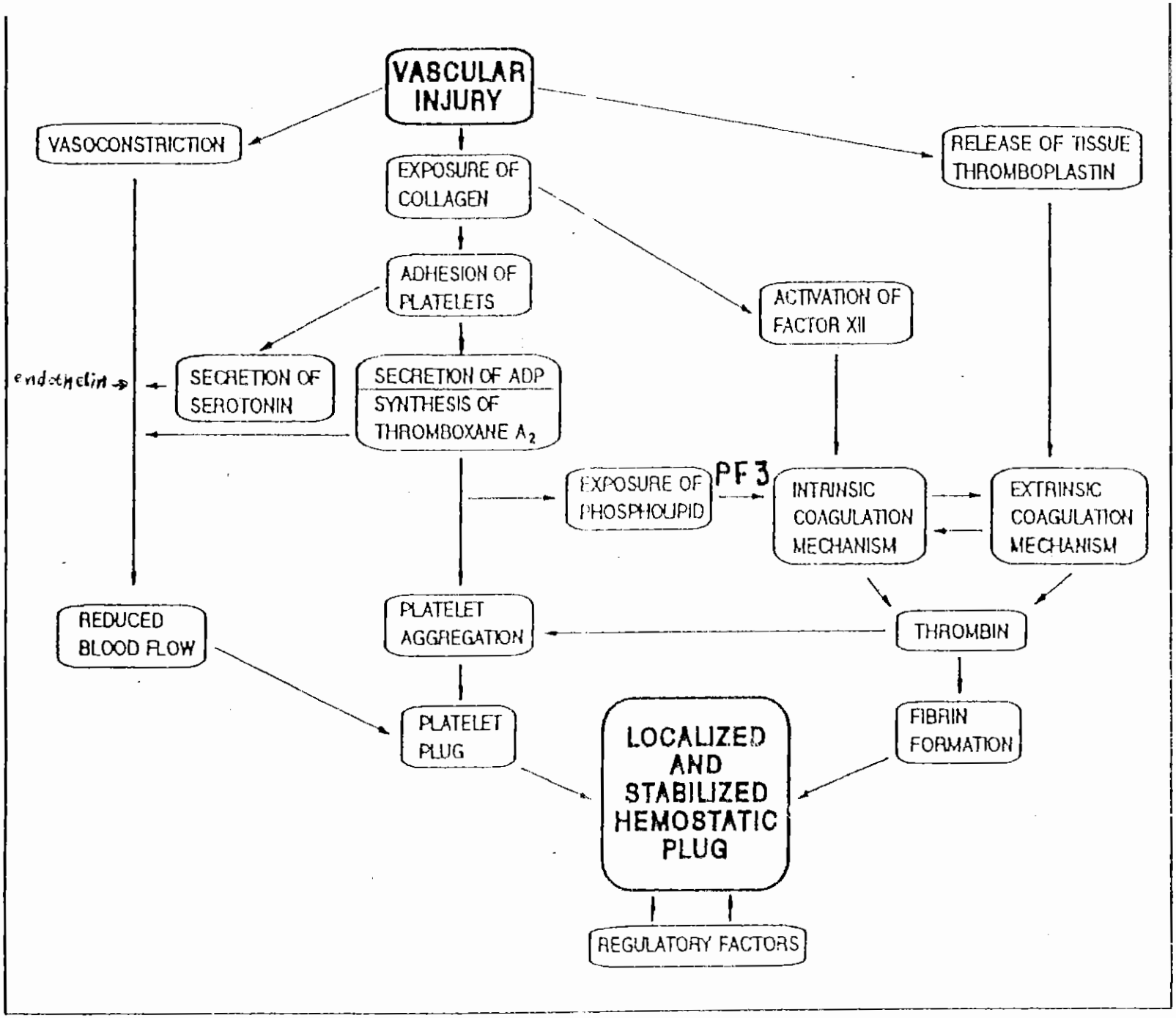


Fig. 25-4. Summary of the integrated hemostatic response to vessel injury. (See text description.)

Table 10.1 Major blood clotting factors

Factor	Name (synonyms)	Site of formation
I	Fibrinogen	Liver
II[a]	Prothrombin	Liver
III	Tissue thromboplastins	Tissue cells (membrane protein)
IV	Calcium ions	
V[b]	Labile factor	Mainly liver
VII[a]	Stable factor	Liver
VIII[b]	Anti-haemophiliac globulin A (AHG)	Platelets, RES endothelial cells, liver
vWF	von Willebrand's factor	Endothelial cells, platelets
IX[a]	Anti-haemophiliac globulin B (Christmas factor)	Liver
X[a]	Stuart factor	Liver
XI	Plasma thromboplastin antecedant factor (PTA)	Liver
XII	Hageman factor	Liver
XIII	Fibrin stabilizing factor	Liver
TF3	Platelet factor 3	Platelets

Note
[a] vitamin K-dependent [b] pro-cofactors

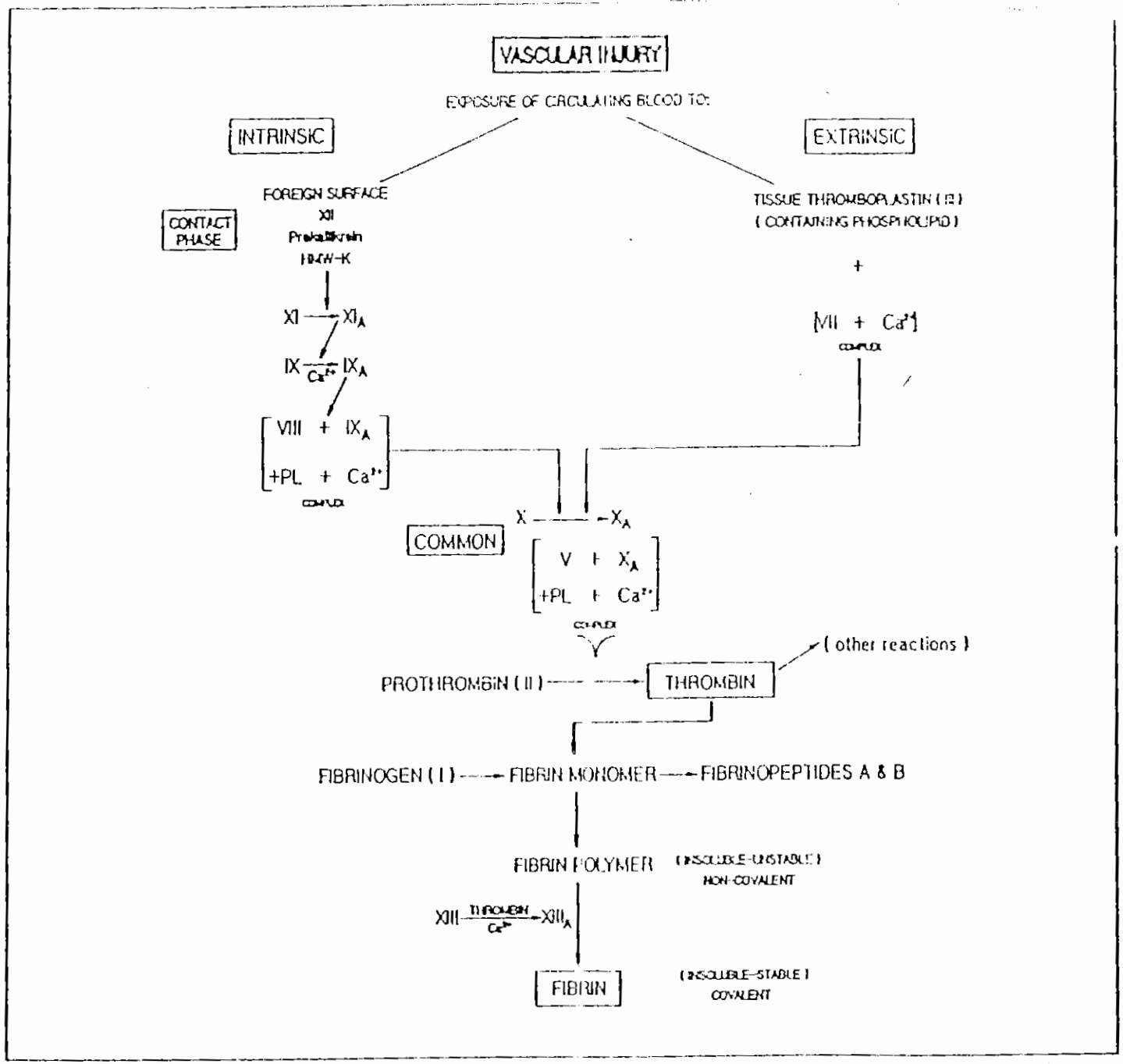


Fig. 24-5. The intrinsic, extrinsic, and common enzymatic pathways of blood coagulation. (See text for detailed description.) (*HMW-K* = high-molecular-weight kininogen; *PL* = phospholipid.)

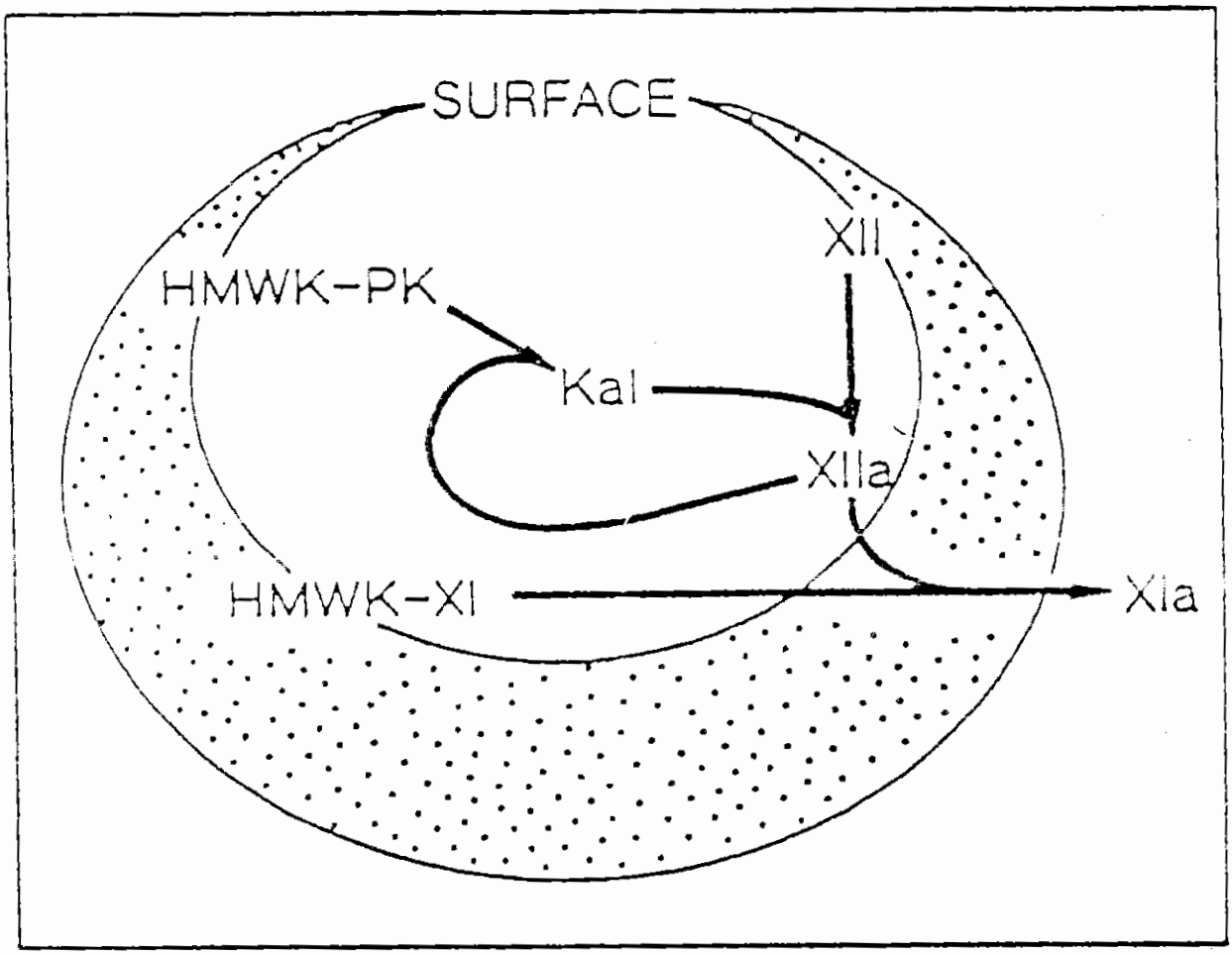


Fig. 24-6. The contact phase of blood coagulation, showing the reactions leading to the activation of factor XI when blood is exposed to a negatively charged foreign surface. (See text for the other explanation.) (*HMWK* = high-molecular-weight kininogen; *PK* = prekallikrein; *Kal* = kallikrein.)

Additional points on the clotting system

1 Both intrinsic and extrinsic pathways are necessary for normal haemostasis.

2 Both pathways are activated when blood leaves the blood-vessels for the tissues.

3 Thrombin is a key factor in both the intrinsic and extrinsic systems, in addition to its action on fibrinogen.

4 The activation of the clotting mechanism along the shorter extrinsic pathway results in the rapid formation of thrombin, which feeds back to activate the intrinsic pathway through factors VII and V. Factor VII can activate factor X to active factor X, and this forms an activation connection between both pathways.

5 Thrombin stimulates platelets to release ADP and TXA_2 and therefore enhances further aggregation of platelets.

6 Thrombin is essential for platelet morphological changes during haemostasis, which lead to the formation of the primary haemostatic plug.

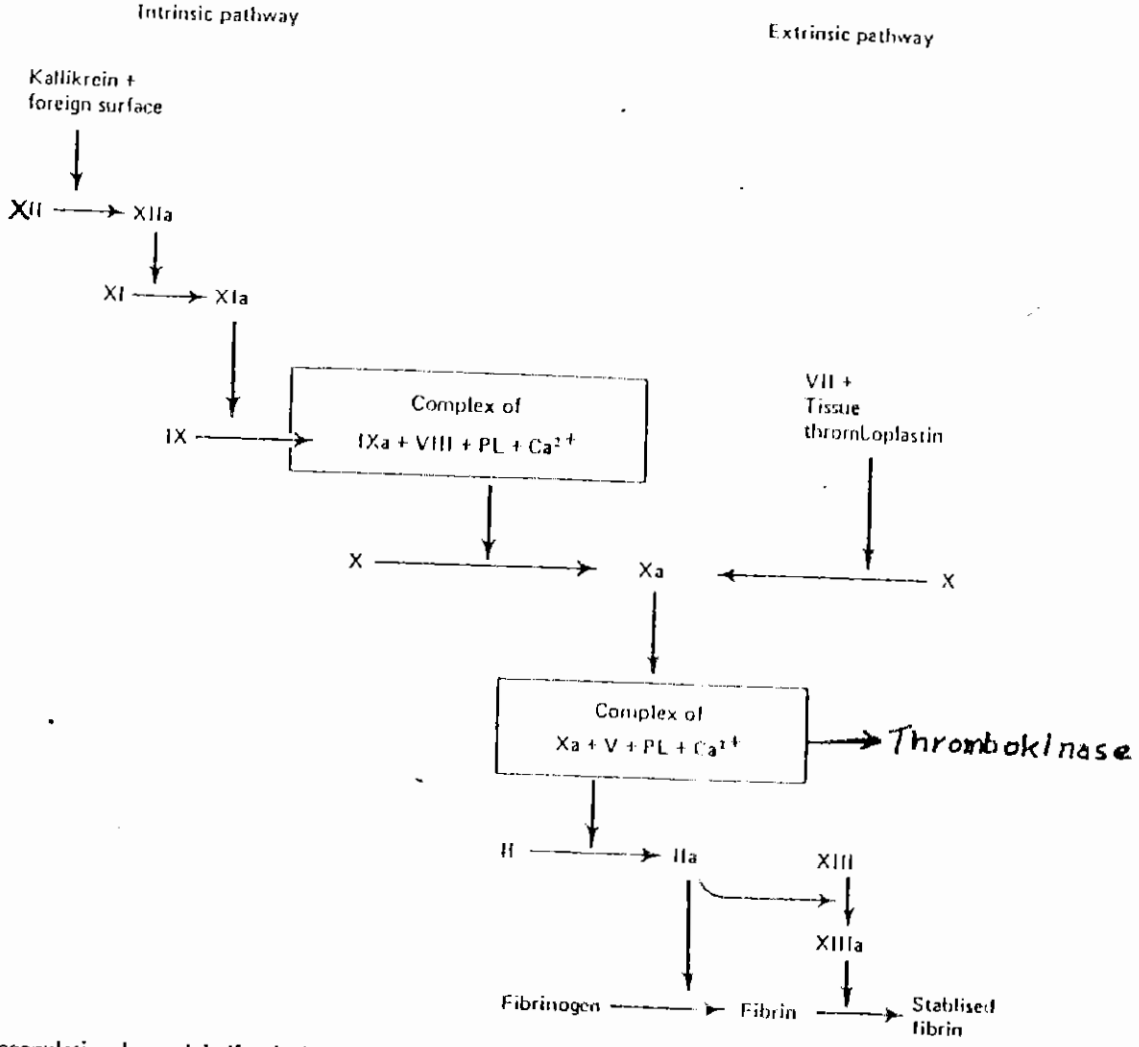
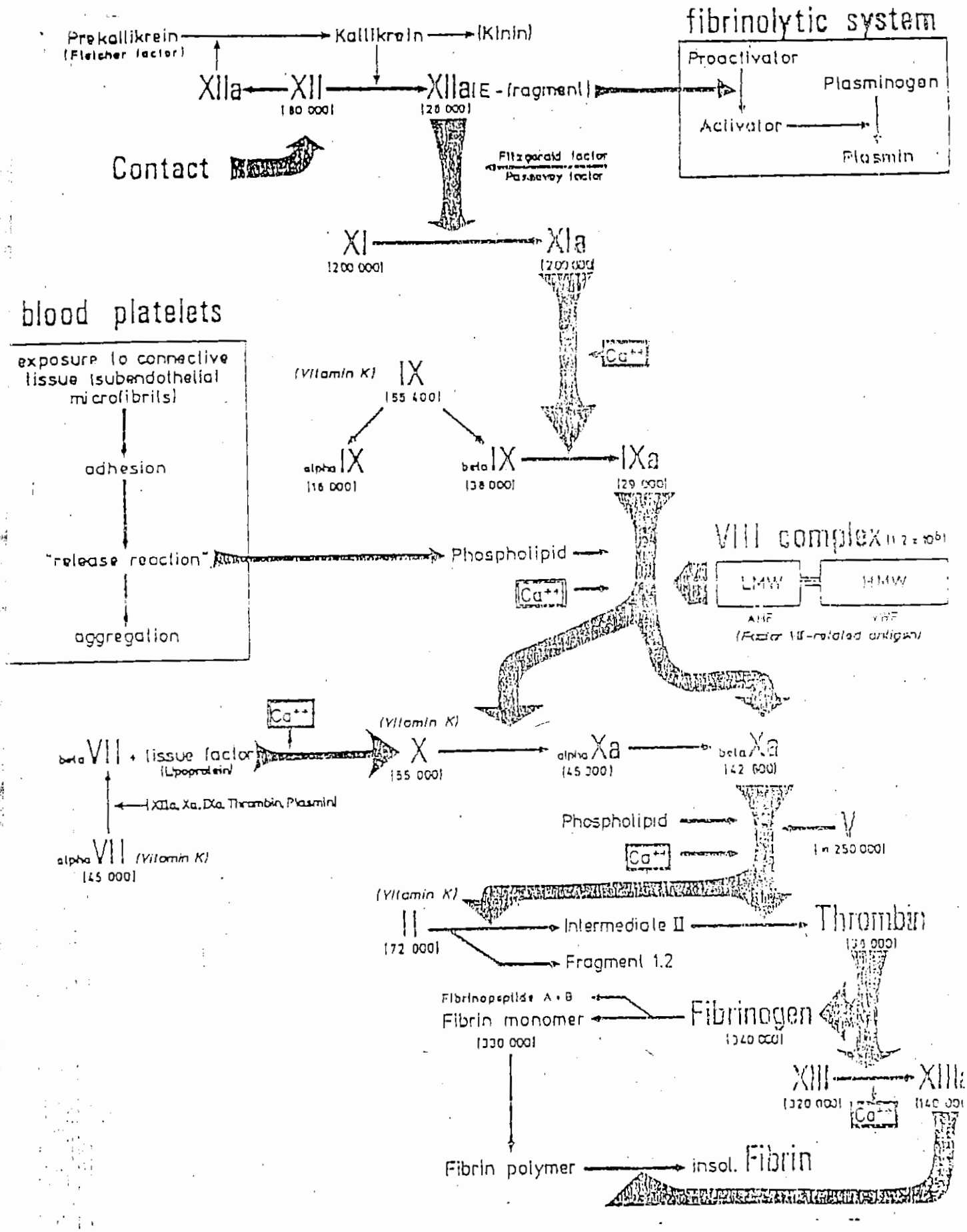


Fig. 4.21 The coagulation 'cascade'. 'Intrinsic' means intrinsic to plasma since all the factors can be generated from plasma. The extrinsic pathway requires tissue factors from outside the plasma. Extrinsic coagulation is more rapid and less inhibited than the intrinsic process, fewer steps being involved. PL = platelet phospholipid (Factor III)


fibrinolytic system
Prekallikrein
(Fletcher factor)
Kallikrein
(Kinin)
XIIa
XII
[80 000]
XIIa (E - fragment)
[28 000]
Proactivator
Plasminogen
Activator
Plasmin
Contact
Fitzgerald factor
Flaujeac factor
Fletcher factor
XI
[200 000]
XIa
[200 000]
blood platelets
exposure to connective tissue (subendothelial microfibrils)
adhesion
"release reaction"
aggregation
(Vitamin K)
IX
[55 000]
alpha IX
[16 000]
beta IX
[38 000]
IXa
[29 000]
Ca++
Phospholipid
VIII complex
LMW
HMW
AHF
(Factor VIII-related antigen)
beta VII + tissue factor
(Lipoprotein)
X
[55 000]
alpha Xa
[45 000]
beta Xa
[42 000]
(XIIa, Xa, IXa, Thrombin, Plasmin)
alpha VII
[45 000]
V
[ca 250 000]
II
[72 000]
Intermediate II
Fragment 1.2
Thrombin
Fibrinopeptide A + B
Fibrin monomer
[330 000]
Fibrinogen
[340 000]
XIII
[320 000]
XIIIa
Fibrin polymer
insol. Fibrin

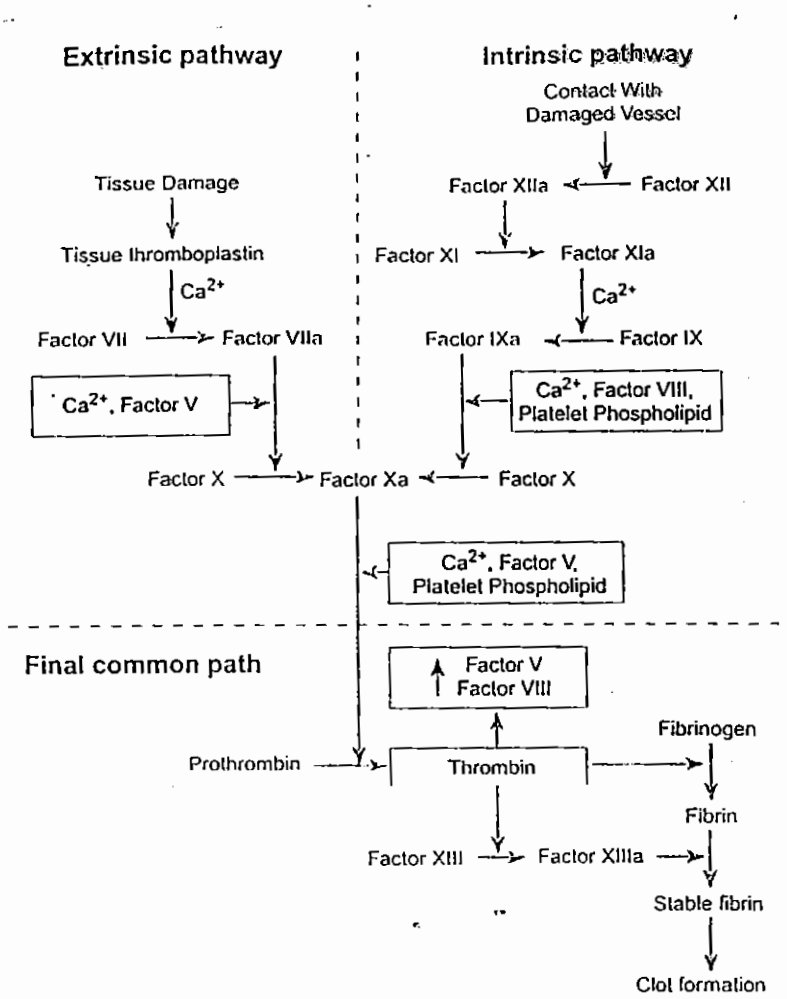


Fig. 13.11 The extrinsic and intrinsic pathways leading to the formation of a blood clot. Note the central roles played by Factor Xa and thrombin in the process of blood coagulation.

The role of calcium in hemostasis

As Fig. 13.11 shows, calcium ions are required for each step in the clotting process except for the first two reactions of the intrinsic pathway. Adequate levels of calcium ions are therefore necessary for normal clotting. In reality, plasma calcium levels never fall low enough to impair the clotting processes since death would have resulted from other causes (most notably tetany of the respiratory muscles) long before. It is, however, possible to prevent the coagulation of blood removed from the body and stored *in vitro* by reducing the calcium ion concentration of the plasma. This may be achieved by the addition of substances such as EDTA (ethylenediaminetetraacetic acid) or citrate, which bind calcium.

BLOOD COAGULATION

The coagulation reaction may be initiated in two different ways. The first is by exposure of the plasma to a foreign surface, that is a surface bearing a negative electrical charge, which in some way causes alteration and activation of factors XI and XII. The product of this reaction is activated factor XI - usually designated as XIa which then acts on factor IX to give IXa.* Factor IXa then combines with factor VIII and with phospholipid from platelets to activate factor X.* Factor X similarly complexes with factor V, calcium and phospholipid to form thrombokinase (sometimes called thromboplastin). Thrombokinase activates factor II (prothrombin) to form thrombin.* It will be noted that apart from the 'foreign surface' all the components of this reaction chain are contained in the blood, hence the name intrinsic coagulation system. In the second coagulation reaction, the extrinsic system, the surface activated reactions of the intrinsic system are bypassed; phospholipid and protein from injured tissue (also sometimes called thromboplastin) combine with calcium to activate factor X; from this point onwards the reactions are as in the intrinsic system. In both systems the function of the phospholipid seems to be physical rather than chemical, the lipid-protein micelles forming a suitable surface on which the reactions may take place.

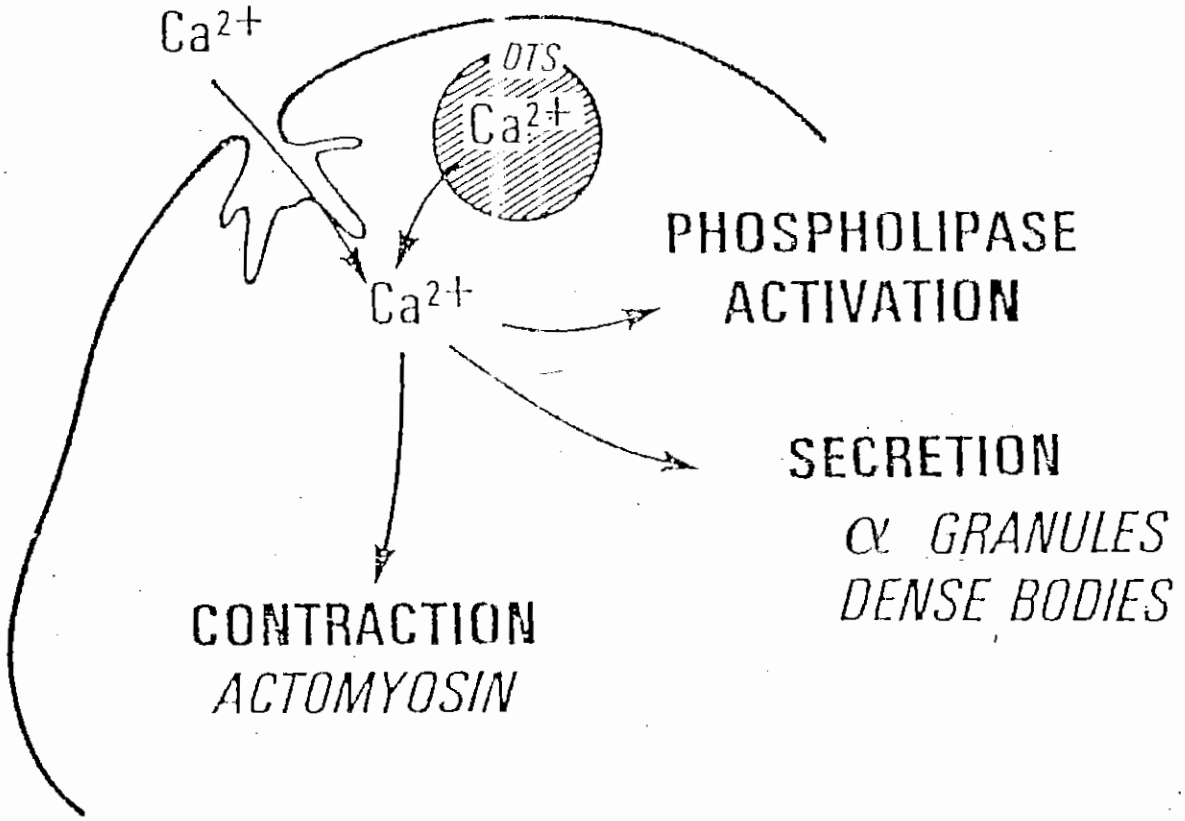


Figure 3.32. The flow of calcium into the cytoplasm of the platelet after stimulation and responses that this inititates. DTS, dense tubular system.

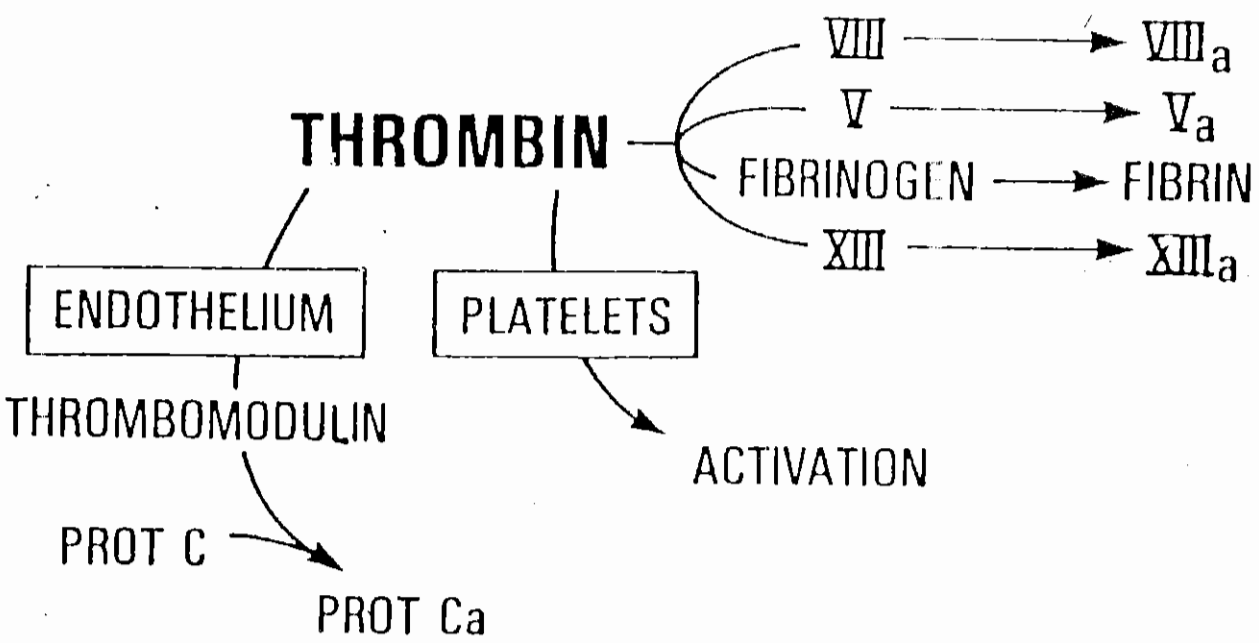


Figure 3.27. The multiple actions of thrombin in blood coagulation. *Prot C*, protein C; *Prot Ca*, activated protein C.

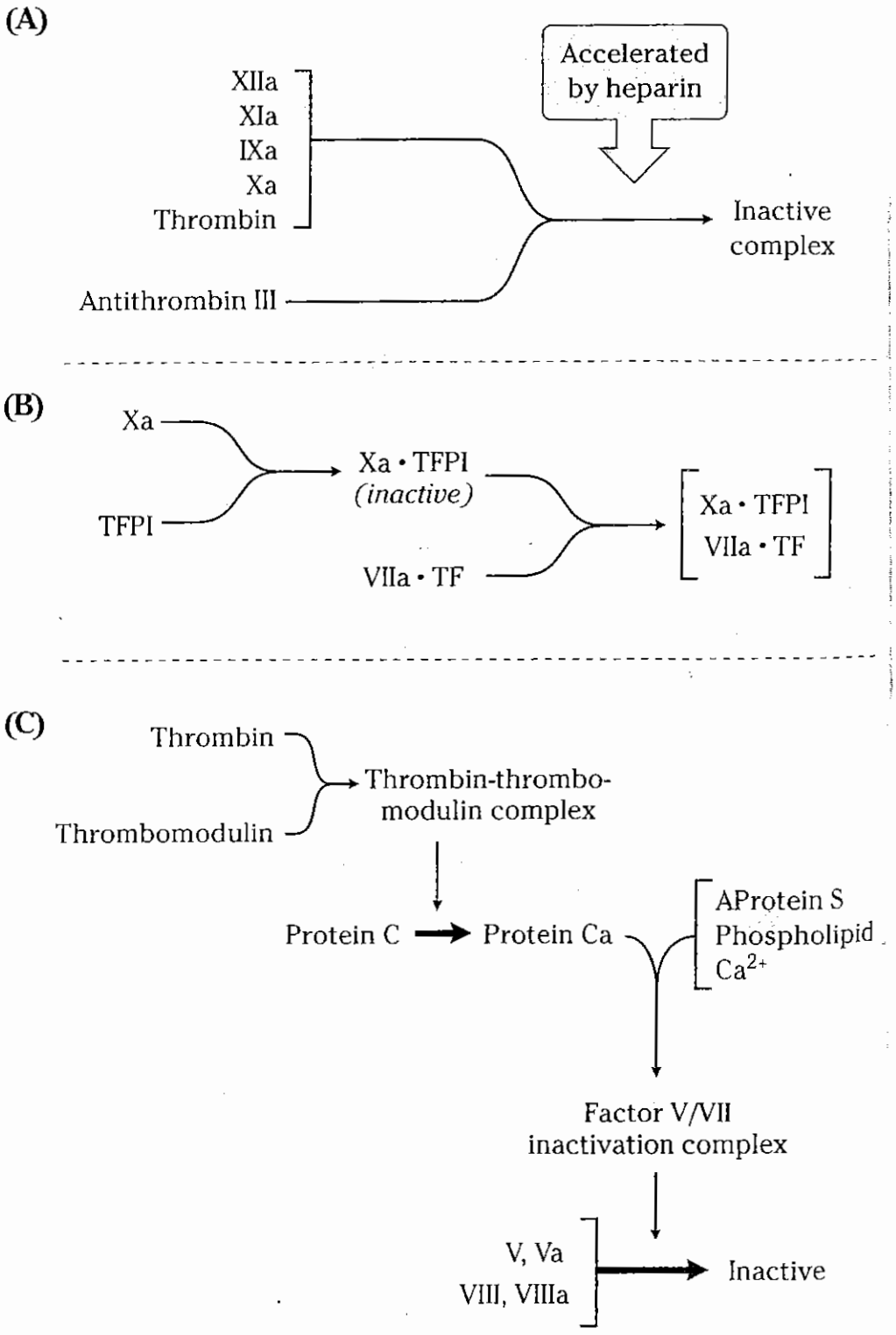


Figure 10.5 The natural anticoagulant mechanisms. The three mechanisms inhibit the clotting cascade by degrading or inactivating activated factors. **A,B.** The antithrombin III system and the TFPI system both inactivate factor Xa, the first member of the common final pathway. **C.** The powerful proteins C and S system, while largely restricted to factors V and VIII, can degrade both the active forms and the proenzymes.

Causes of Normal Fluidity of Blood

In healthy conditions, blood does not clot inside vessels because:

1. heparin is present in plasma.
2. clotting factors, e.g. prothrombin & fibrinogen exist in plasma in an inactive from , or removal of some from the circulation by the liver.
3. the blood clotting factors are also reduced to some extent that they are used up during clotting.
4. the liberation from clotting blood of substances that inhibit further clotting (fibrin or fibrinogen degradation products.
5. endothelial lining of vessel is smooth no sticking of platelets to it because both the lining & the platelets have negative charges repelling platelets away from lining.
6. antithrembin III: inhibits the action of thrombin as well as 1Xa, Xa , X1a & X11a.
7. thrombin is bound by a specific receptor on endothelial cells, thrombomodulin. The result of this interaction is conversion of circulating protein C to its active form, Ca , protein Ca in the presence of phospholipid, Ca^{2+} & a co-factor, protein S, inactivates factor V & VII & thus limits the generation of thrombin. Proteins C & S require vitamin K for their synthesis in the liver & protein Ca also enhances fibrinolysis.
8. two other proteins, α_2 -macroglobulin &α_1 antitrypsin, also contribute to the antithrombin effect of plasma.
9. fibrinolytic system.

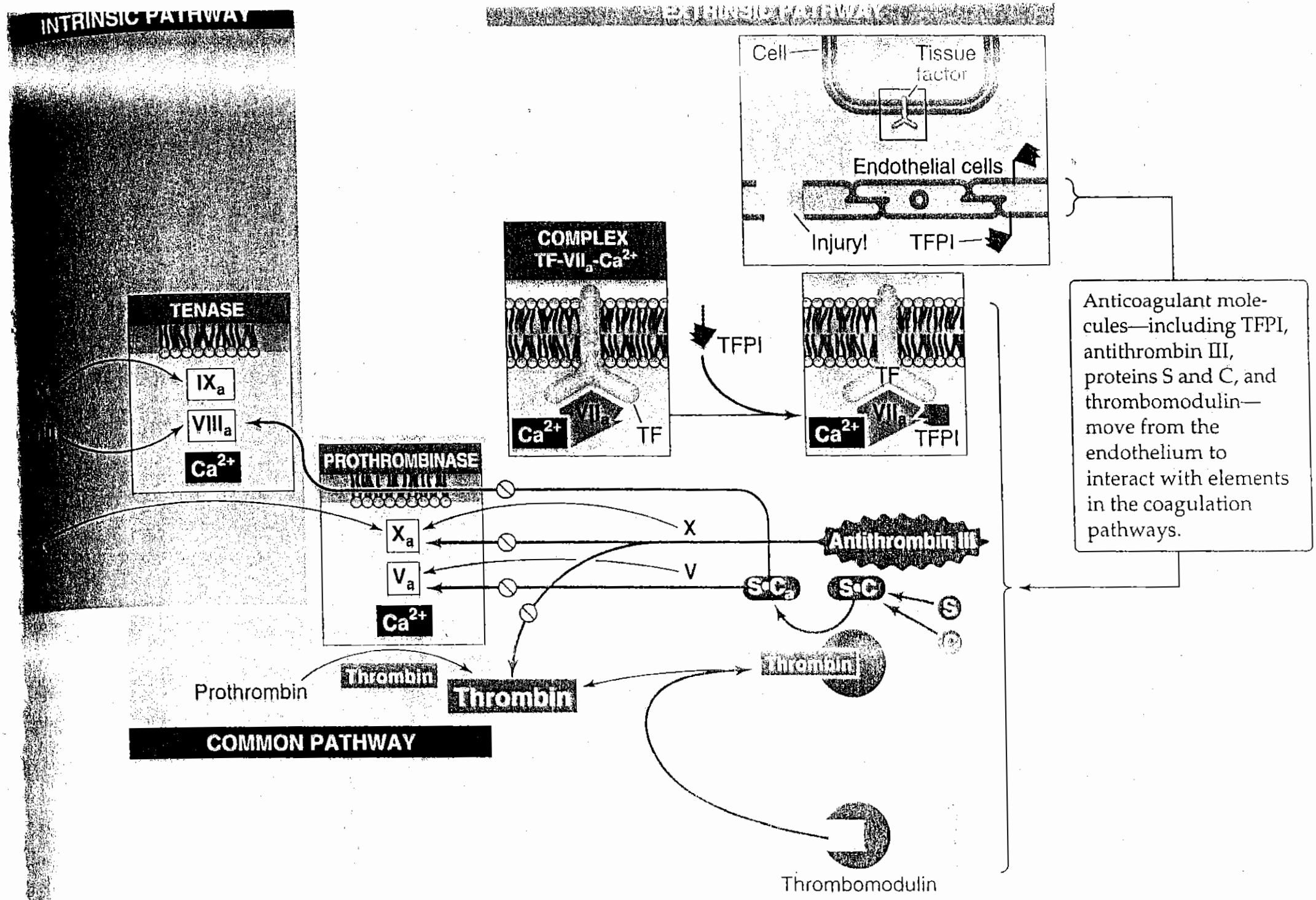


Figure 18-13 An abbreviated version of the coagulation cascade, showing the anticoagulant factors. The anticoagulant pathway [illegible]

Clot retraction

Following the coagulation of blood, the clot gradually shrinks as *serum* is extruded from it. The exact mechanism of this process is not understood but it is believed to be initiated by the action of thrombin on platelets. One idea is that thrombin causes the release of intracellularly stored calcium into the platelet cytoplasm. This calcium then triggers the contraction of contractile proteins within the platelets by a process resembling the contraction of muscle. The contractile process may then cause the extrusion of pseudopodia from the platelets. These stick to the fibrin strands within the clot and, as they contract, the fibrin strands are pulled together, at the same time squeezing out the entrapped fluid as serum.

Dissolution of the clot

Once the wall of the damaged blood vessel is repaired, the blood clot is removed by lysis. Activated Factor XII stimulates the production of a substance in the plasma known as *kallikrein*. In turn, kallikrein promotes the conversion of inactive *plasminogen* into active *plasmin*, an enzyme that digests fibrin and thus brings about dissolution of the clot.

Various other plasminogen activators are used clinically to promote the dissolution of clots. These include *streptokinase*, a substance produced naturally by certain bacteria, and an endogenous substance called *tissue plasminogen activator* (TPA) which can now be produced commercially by genetic engineering. These substances can be injected either into the general circulation or into a specific blood vessel that contains a clot to promote lysis of the clot.

FIBRINOLYSIS

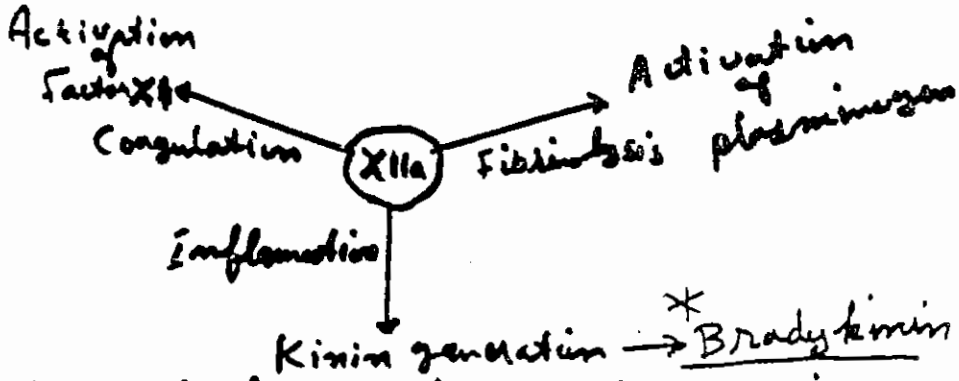
(1) Fibrinolysis (like Coagulation) is a normal haemostatic response to vascular injury.

(2) Plasminogen, a beta globulin pro-enzyme in blood and tissue fluid. It is made by the liver and to a lesser extent by eosinophils and by intravascular endothelium.

(3) Plasminogen is converted to Plasmin by activators either from the vessel wall (intrinsic activation) or from the tissues (extrinsic activation)

(4) Release of circulating Plasminogen activator from endothelial cells occurs after such stimuli as trauma, exercise or emotional stress.

(5) Activated factor XII also Potentiates the action of Plasminogen activator.



* The central role of F. XII in reactions of Coagulation, Fibrinolysis and inflamation

* Bradykinin: Increases Vascular permeability and is a vasodilator.

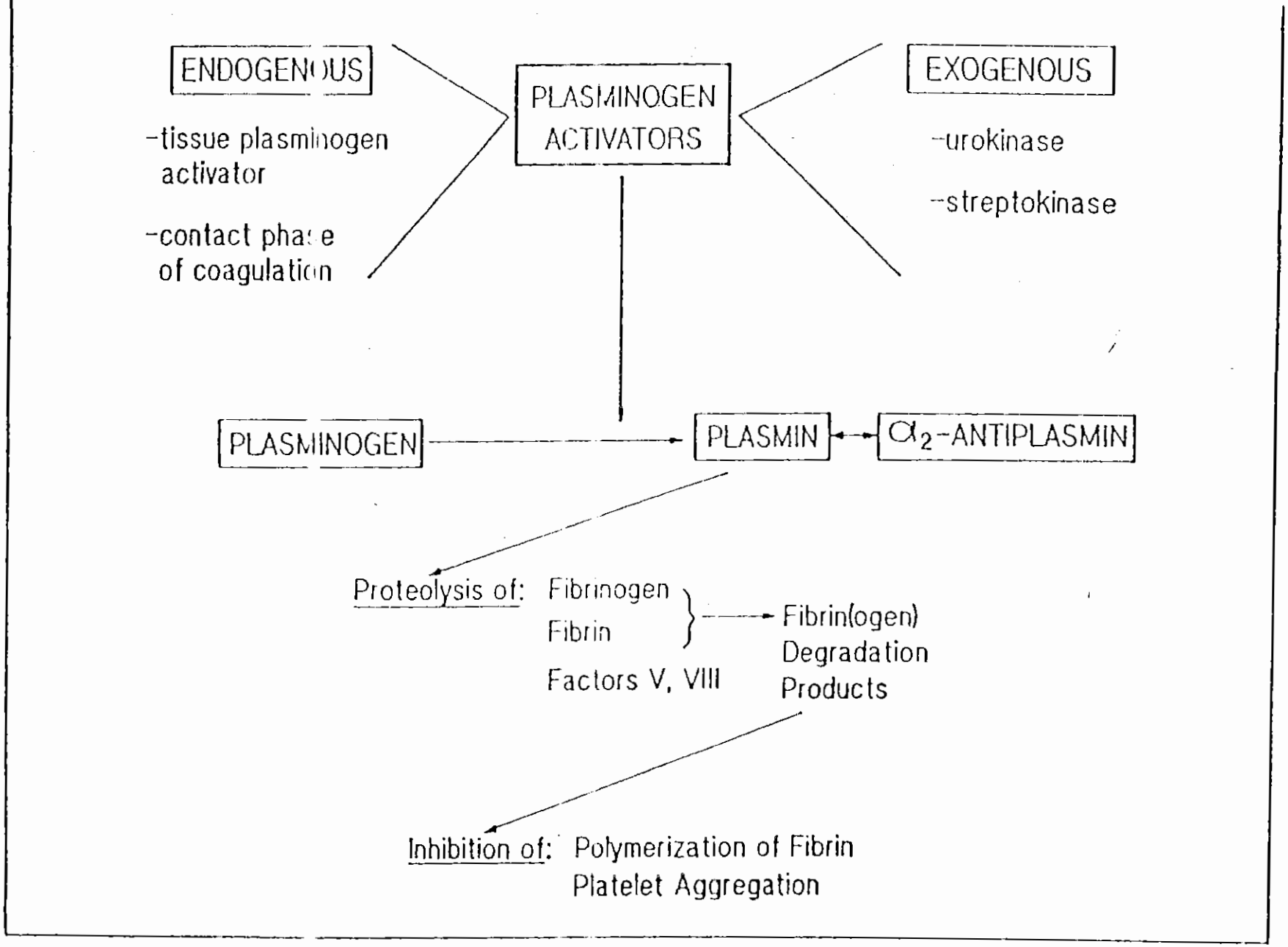


Fig. 25-1. The components of the fibrinolytic enzyme system. (See text for elaboration.)

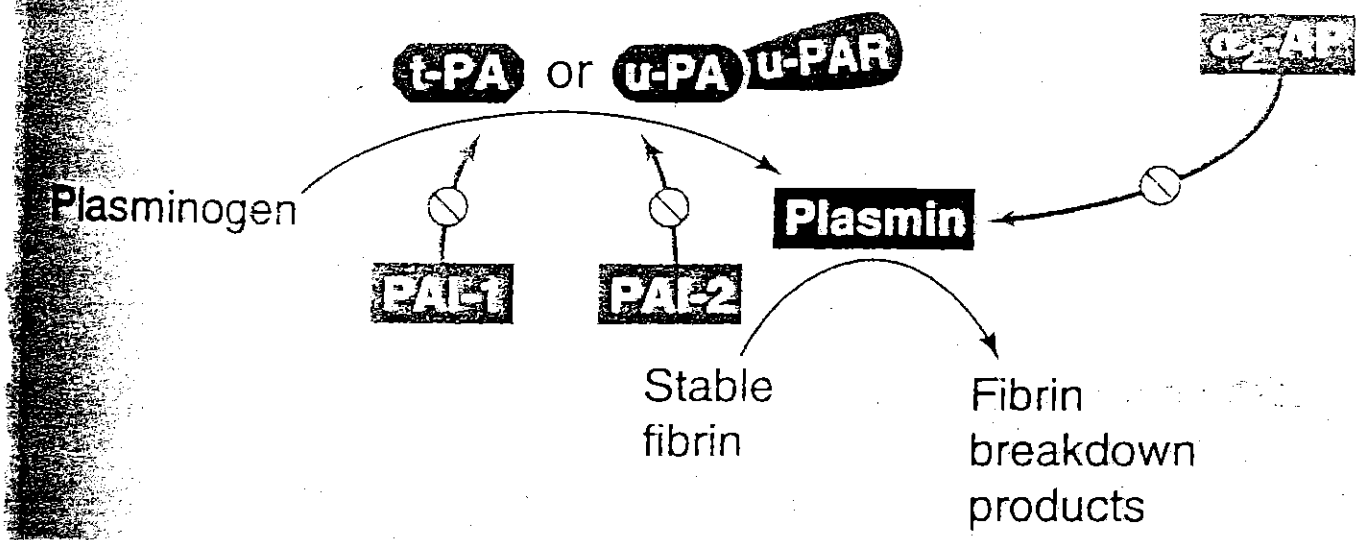


Figure 18-14 The fibrinolytic cascade.

CLASSIFICATION OF HAEMOSTATIC DEFECTS

Although the action of platelets, the clotting mechanism and the integrity of th vascular wall are all closely related in the prevention of bleeding, it is convenien to consider that abnormalities in haemostasis arise from defects in one of thes three processes. The commonest cause of bleeding is undoubtedly a deficiency of platelets, the second commonest cause is an abnormality in the clotting mechanism. The remaining patients do not have any demonstrable lesion of the platelets or clotting mechanism and appear to be bleeding as a result of vascular abnormalities.

Thrombocytopenic purpura

When the platelet count is low, clot retraction is deficient and there is poor constriction or ruptured vessels.Is characterized by easy bruisability and multiple subcutaneous hemorrhages

Thrombasthenic purpura .

Purpura may also occur when the platelet count is normal, and in some of these cases, the circulating platelets are abnormal

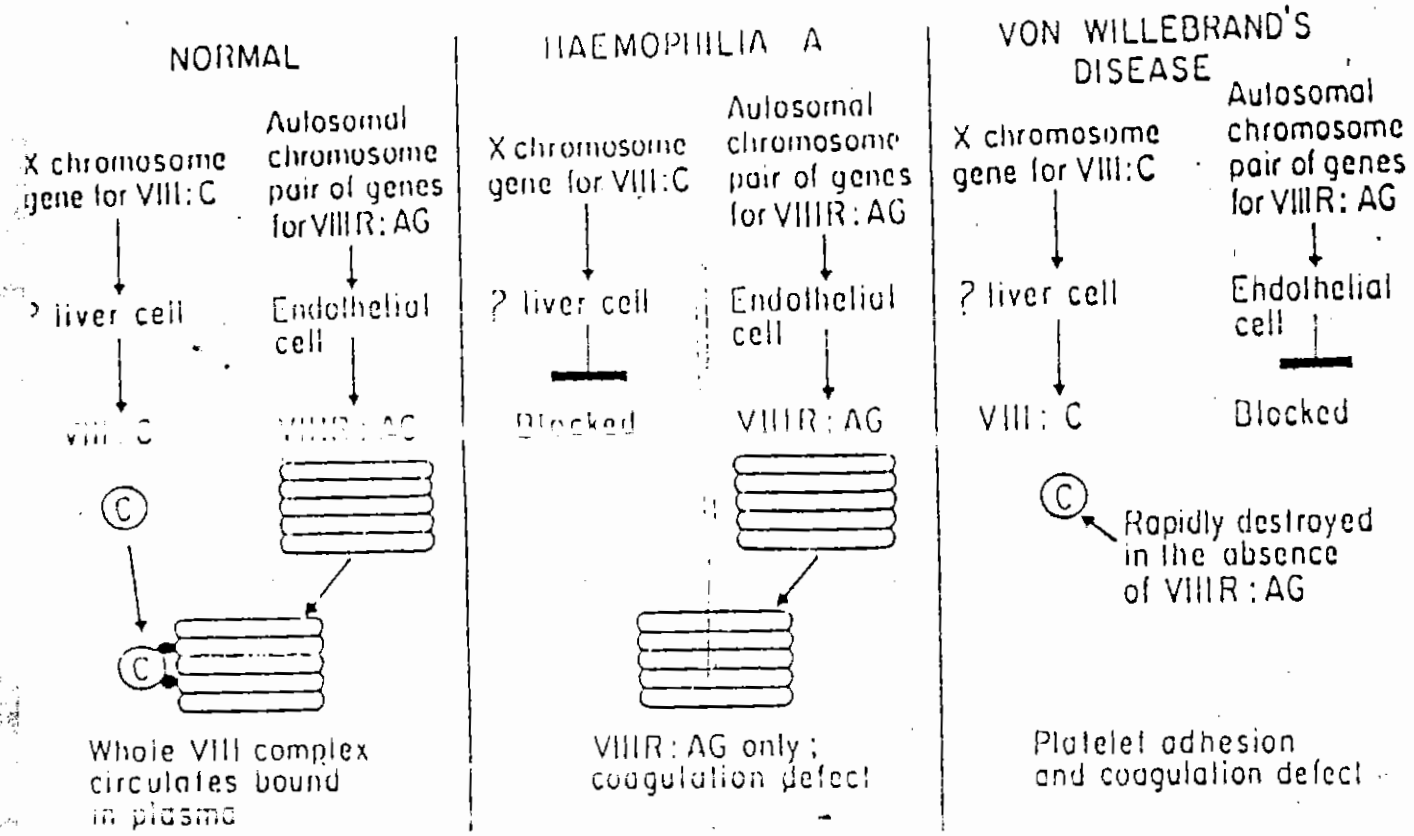


Fig. 13.2 The synthesis of factor VIII in normal individuals, in haemophilia A and in von Willebrand's disease.

Clinical features

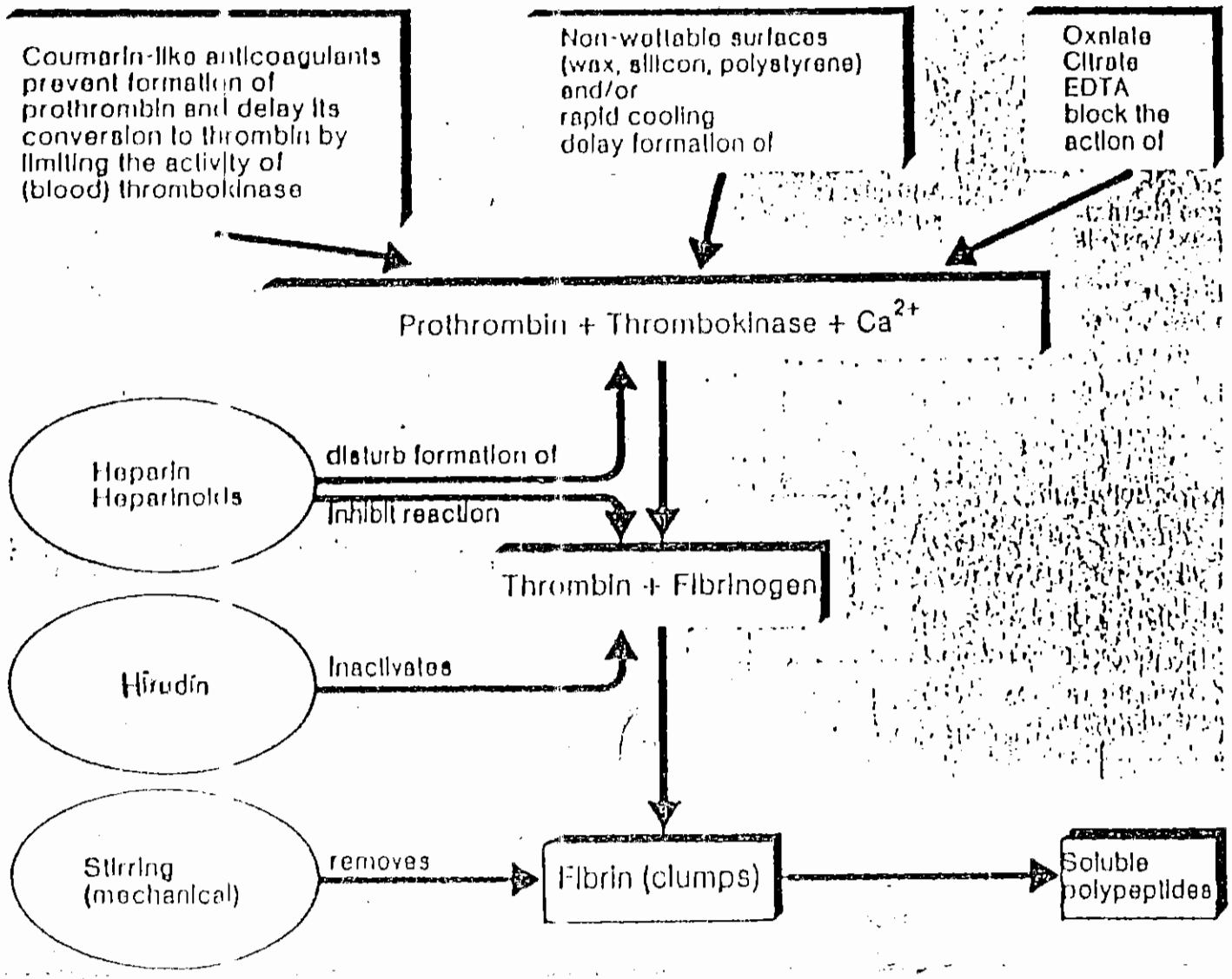
Severely affected infants may suffer from profuse post-circumcision haemorrhage. Prolonged bleeding occurs after dental extractio Operative and post-traumatic haemorrhage are life-threatenin both in severely and mildly affected patients.

Table 13.2 Main clinical and laboratory findings in haemophilia A, factor IX deficiency (haemophilia B, Christmas disease) and von Willebrand's disease.

	Haemophilia A	Factor IX deficiency	Von Willebrand's disease
Inheritance	Sex-linked		Dominant
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Factor VIII:C	Low	Normal	Low
Factor VIII:AG	Normal	Normal	Low
aggregation	Normal	Normal	Impaired

Hereditary Disorders of other Coagulation Factors:

1- All these disorders are rare.
2- In most inheritance is autosomal.
3- There is usually a good correlation between the patient's symptoms and the severity of the coagulation deficiency.
4- F. XII deficiency is not associated with abnormal bleeding
5- F. XI deficiency produces mild symptoms. (Haemophilia C)
6- F. XIII deficiency produces severe bleeding tend


Coumarin-like anticoagulants prevent formation of prothrombin and delay its conversion to thrombin by limiting the activity of (blood) thromboklnase
Non-wettable surfaces (wax, silicon, polystyrene) and/or rapid cooling delay formation of
Oxalate Citrate EDTA block the action of
Prothrombin + Thromboklnase + Ca^{2+}
Heparin Heparinoids
disturb formation of
inhibit reaction
Thrombin + Fibrinogen
Hirudin
inactivates
Stirring (mechanical)
removes
Fibrin (clumps)
Soluble polypeptides