Platelet Disorders

TUCOM
Dep. of Medicine
5th year
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Platelet disorders

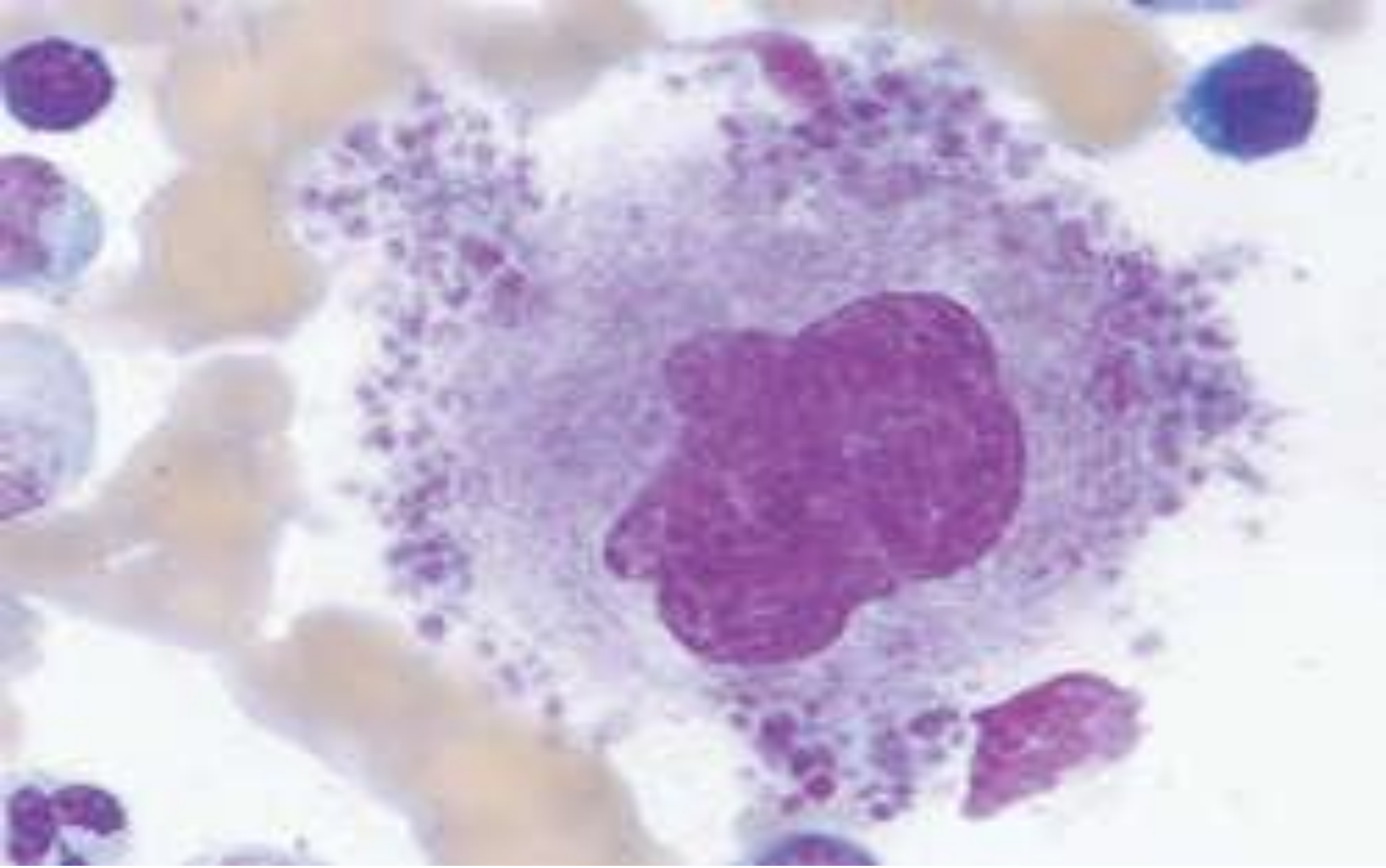
Learning objectives:

1. Review the function of platelets
2. Enumerate the causes, investigations and management of thrombocytopenia
3. Explain the following conditions: idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia and disseminated intravascular coagulation
4. Clarify the platelet function disorders
5. Enumerate the causes of thrombocytosis
6. Show the causes of non-thrombocytopenic purpura

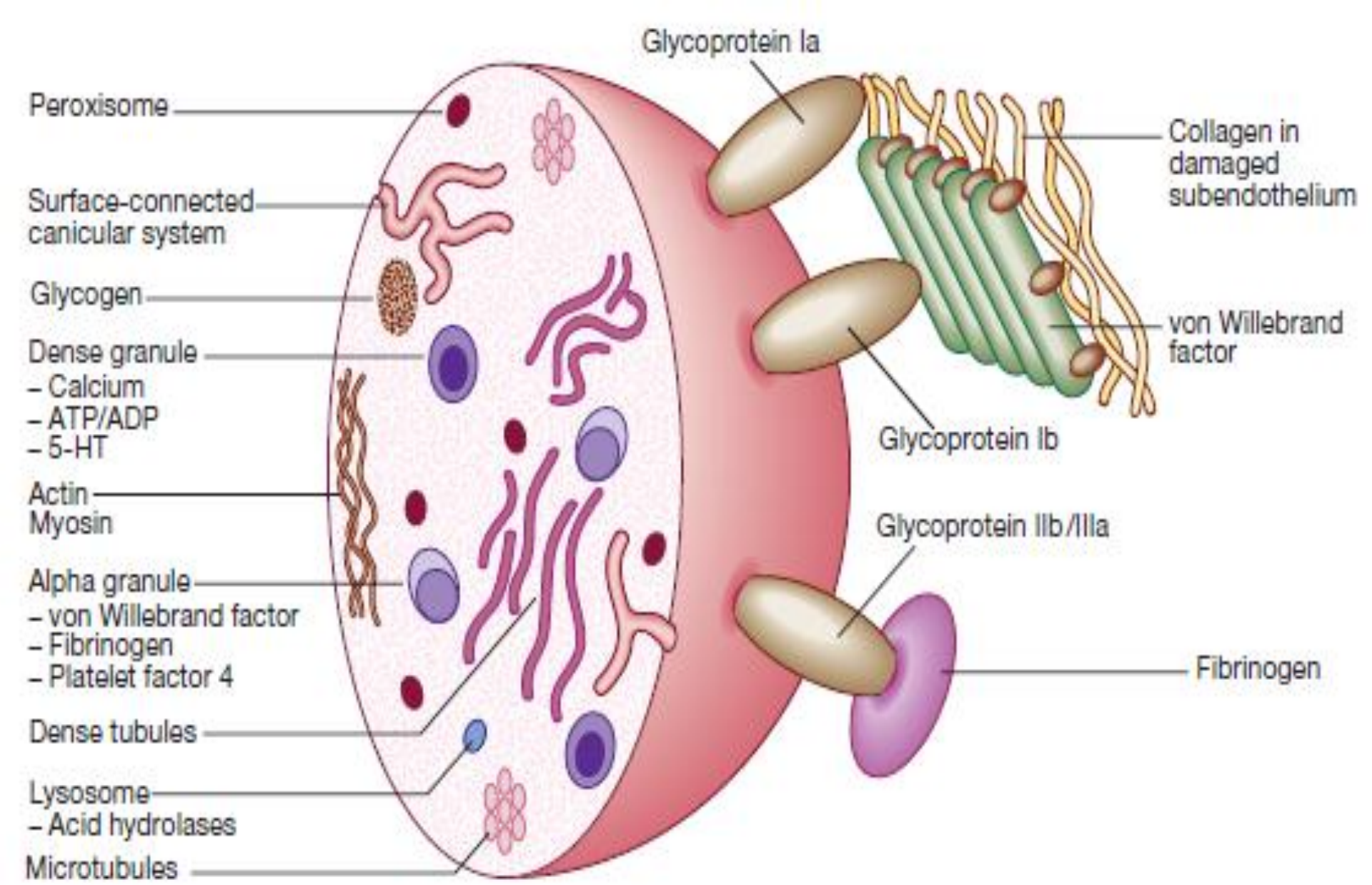
Platelets

Platelets are formed in the bone marrow from megakaryocytes. The formation and maturation of megakaryocytes are stimulated by thrombopoietin, which produced in the liver. When platelets are released into the circulation, they survive between 7 to 10 days. Some 30% of peripheral platelets are normally pooled in the spleen and do not circulate.

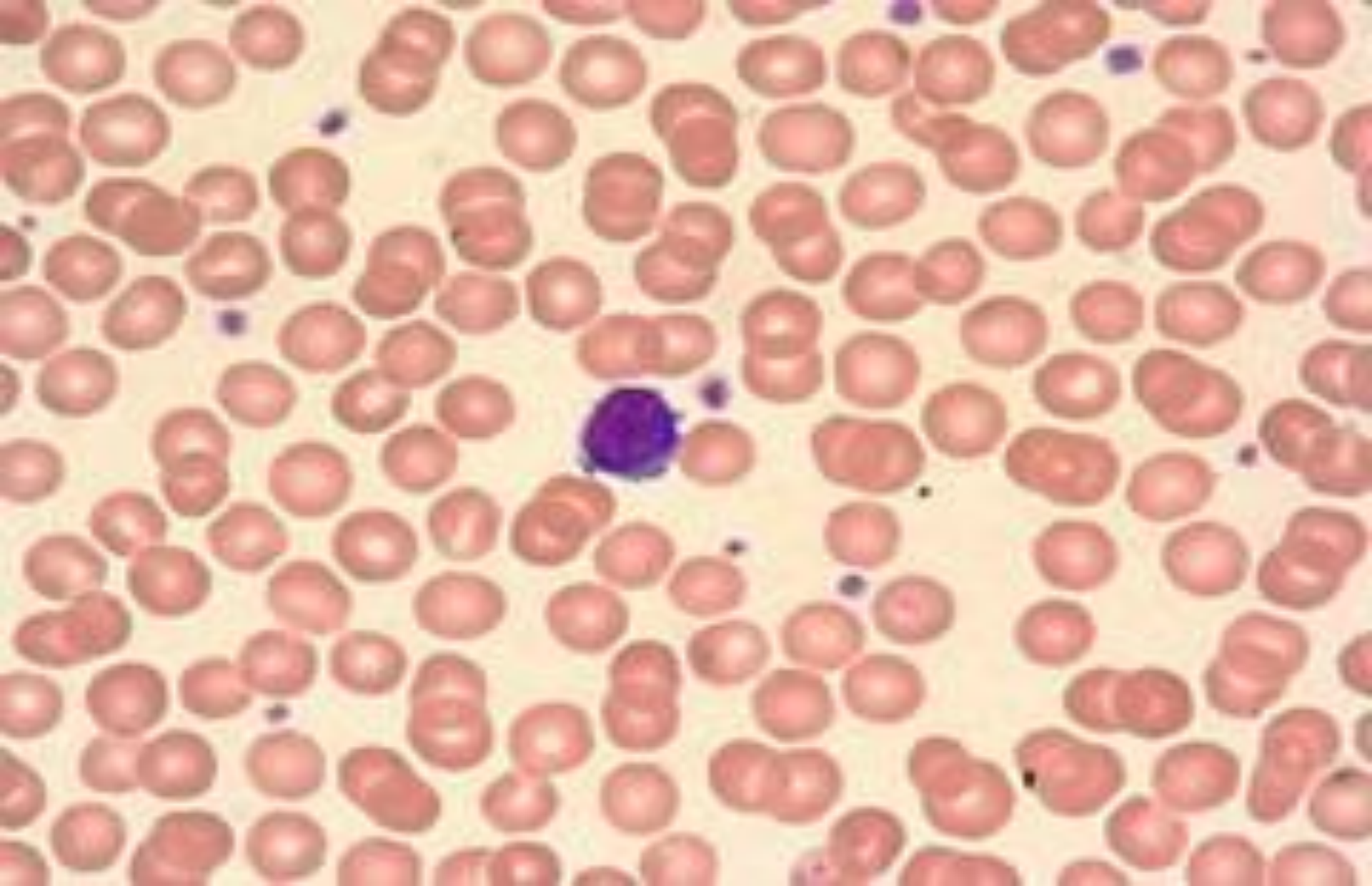
Platelets are anucleate cells, discoid in shape, with a diameter of 2- 4 µm. The surface membrane invaginates to form a tubular network, the canalicular system, which provides a conduit for the discharge of the granule content following platelet activation.



Megakaryocyte: Large bone marrow cell with large or multiple nuclei from which platelets are derived.



Normal platelet structure. (5 HT = 5-hydroxytryptamine, serotonin; ADP = adenosine diphosphate; ATP = adenosine triphosphate



Normal Peripheral Smear: normal red cells, a lymphocyte and platelets

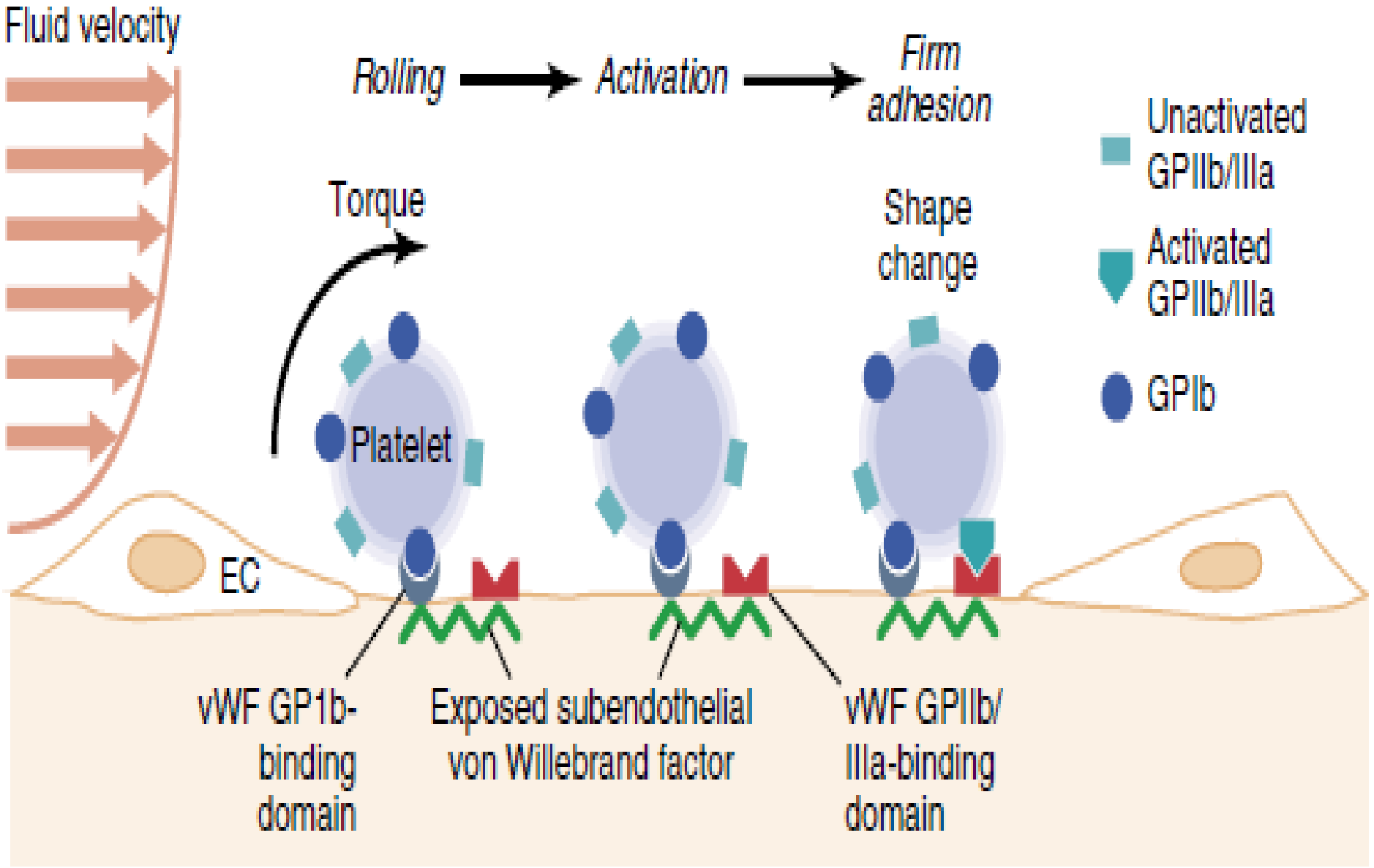
The platelet functions as the cellular-based platform for hemostasis. Platelets mediate primary hemostasis through:

1- Receptors adhesion activation: by binding to endothelium and subendothelium at sites of damage

- **GPIb/IX/V-vWF**
- **GPIIb/IIIa-fibrinogen and GPIIb/IIIa-vWF**
- **GPIa/IIa-collagen**
- **GPV-thrombin**

2- Secreted α-Granule Proteins: fibrinogen, vWF, α2-antiplasmin, factors V, VIII, and XI, Antiheparin (platelet factor 4)

3- Secreted Dense-Granule Agonists: ADP, serotonin



The adhesive interactions producing stable platelet attachment to subendothelial von Willebrand factor (vWF).

The normal platelet count range is between 150,000-450,000 per mm^3 (or microlitre) or 150 - 450 x 10^9/L.

With platelet counts in the normal range and normal platelet function, the bleeding time, is generally less than 8 minutes.

Thrombocytopenia (low platelet count)

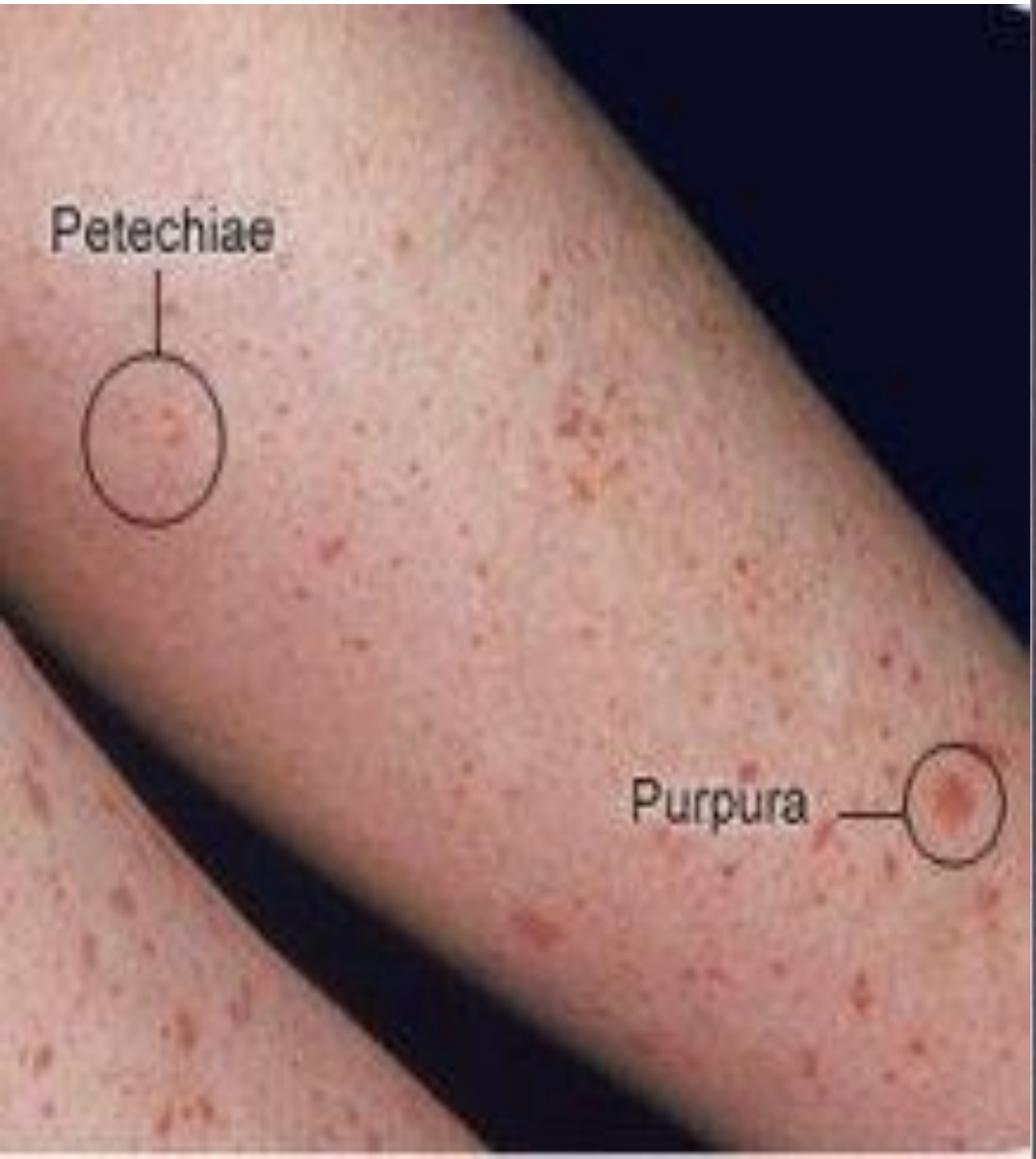
Thrombocytopenia (platelet count <150 x 10^9/L) is one of the most common problems in hospitalized patients.

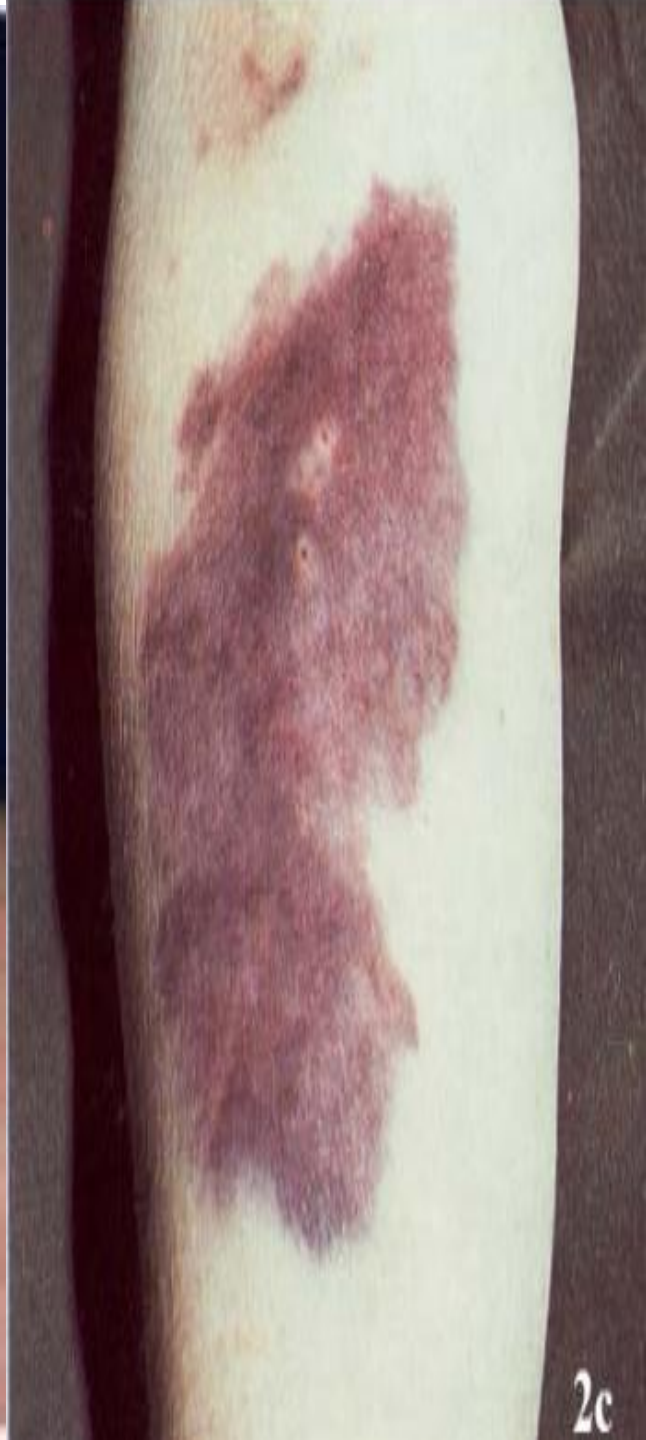
Spontaneous bleeding does not usually occur until the platelet count falls below 20 × 10^9/L.

Patterns of spontaneous bleeding due to thrombocytopenia:

Petechiae: Pinpoint or 1 mm hemorrhages. Purpura: larger (> 3 mm) hemorrhages. Ecchymoses: larger (> 2 cm) hemorrhages. Petechiae, purpura and ecchymoses are not palpable and not blanch when pressed are characteristic, but there may also be oral, nasal, gastrointestinal or genitourinary bleeding.

Severe thrombocytopenia (< 10 × 10^9/L) may result in retinal haemorrhage and potentially fatal intracranial bleeding, but this is rare.


Petechiae
Purpura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Causes of thrombocytopenia

A- Decreased production

1- Marrow hypoplasia: Fanconi's anaemia. Idiopathic aplastic anaemia. Drug-induced: cytotoxics, antimetabolites. Transfusion-associated graft-versus-host disease.

2- Marrow infiltration: Leukaemia. Myeloma. Carcinoma (rare). Myelofibrosis. Osteopetrosis. Lysosomal storage disorders, e.g. Gaucher's disease.

3- Haematinic deficiency: Vitamin B12 and/or folate deficiency

4- Familial (macro-) thrombocytopathies: Alport's syndrome. Bernard Soulier disease. Wiskott–Aldrich syndrome.

B- Increased consumption

1- Immune mechanisms: Idiopathic thrombocytopenic purpura. Post-transfusion purpura. Drug-associated, especially quinine and vancomycin. Heparin-induced thrombocytopenia.

2- Coagulation activation: Disseminated intravascular coagulation.

3- Mechanical pooling: Hypersplenism

4- Thrombotic microangiopathies: Haemolytic uraemic Syndrome. Liver disease. Thrombotic thrombocytopenic purpura. Pre-eclampsia

Investigations:

- Are directed at the possible causes.
- A blood film is the single most useful initial investigation.
- Examination of the bone marrow may reveal increased megakaryocytes in consumptive causes of thrombocytopenia, or the underlying cause of bone marrow failure in leukaemia, hypoplastic anaemia or myelodysplasia.

Treatment: (if required) depends on the underlying cause.

Platelet transfusion is rarely required and is usually confined to patients with bone marrow failure and platelet counts below 10×10^9/L, or to clinical situations with actual or predicted serious haemorrhage.

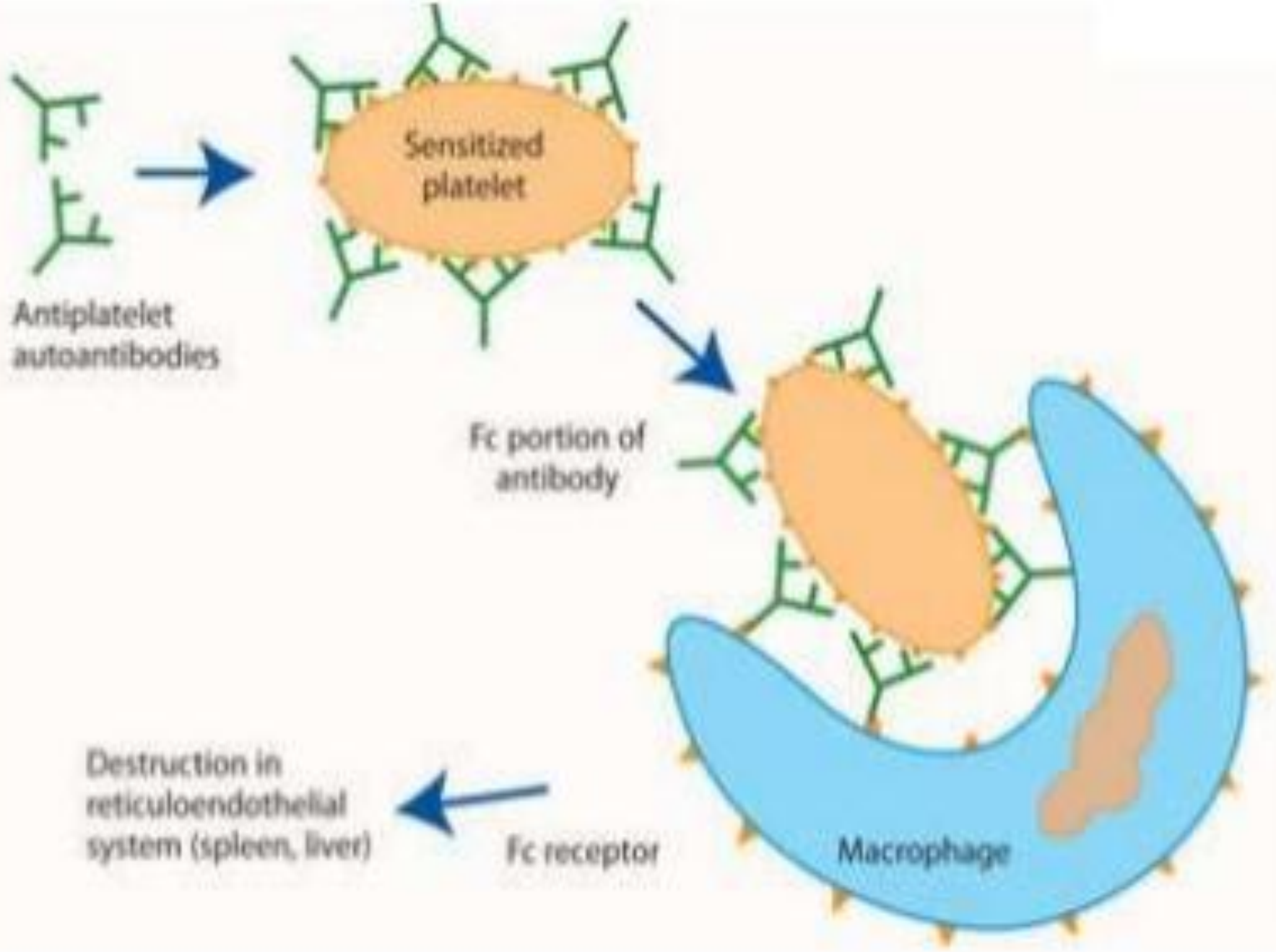
Idiopathic thrombocytopenic purpura (ITP)

ITP: Is an immune mediated by autoantibodies, most often directed against the platelet membrane glycoprotein IIb/IIIa, which sensitise the platelet, resulting in premature removal from the circulation by cells of the reticulo-endothelial system.

It is either occur in isolation or associated with underlying immune dysregulation such as connective tissue diseases, HIV infection, B cell malignancies and pregnancy.

Clinical features:

In children, ITP is usually acute often preceded by a viral infection, such as varicella. In adults, ITP more commonly affects females, an insidious onset and it is unusual for preceding viral infection.


Sensitized platelet
Antiplatelet autoantibodies
Fc portion of antibody
Destruction in reticuloendothelial system (spleen, liver)
Fc receptor
Macrophage

The presentation depends on the degree of thrombocytopenia.

Spontaneous bleeding typically occurs only when the platelet count is below 20×10^9/L.

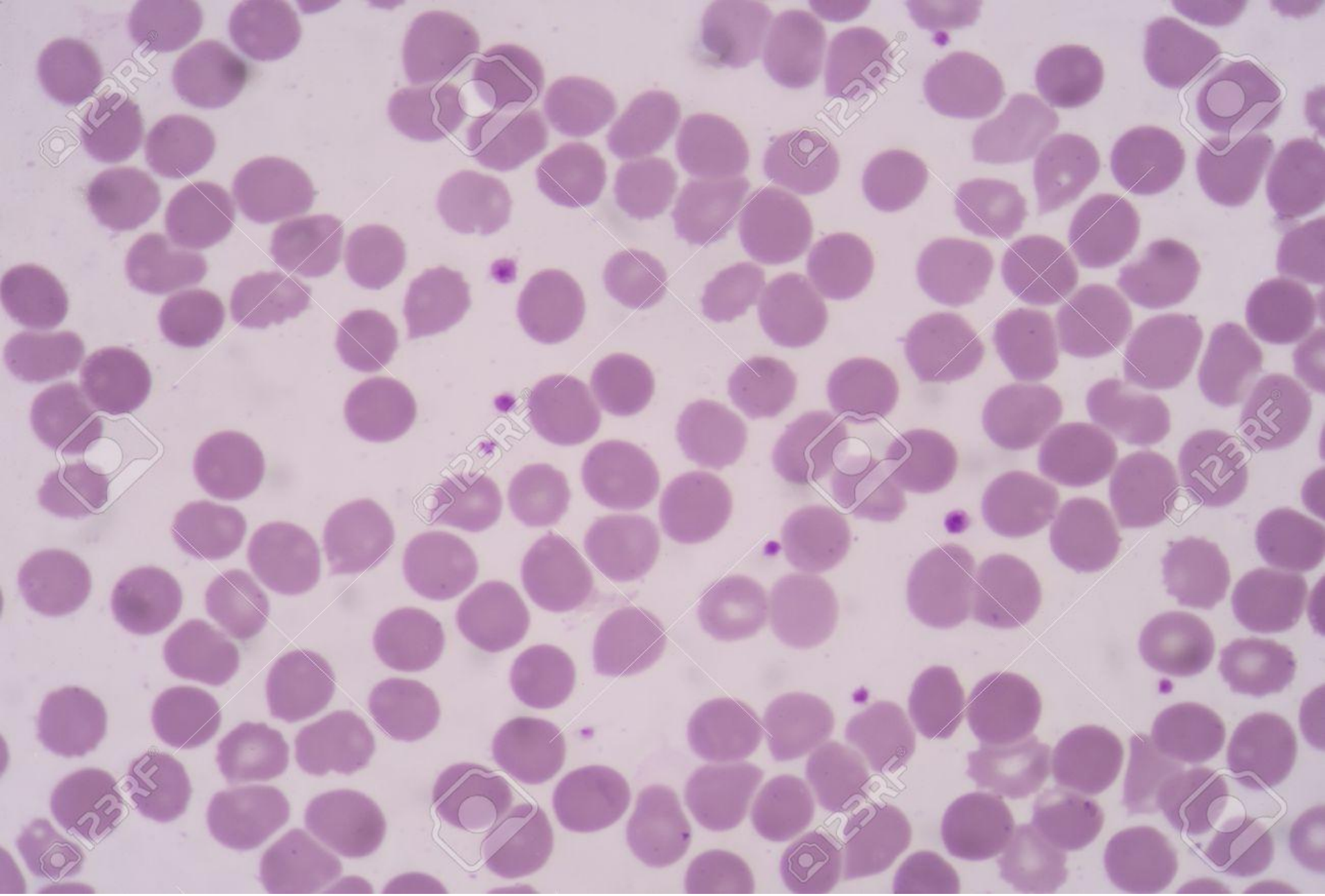
At higher counts, the patient may complain of easy bruising or sometimes epistaxis or menorrhagia.

Many cases with counts of more than 50×10^9/L are discovered by chance.

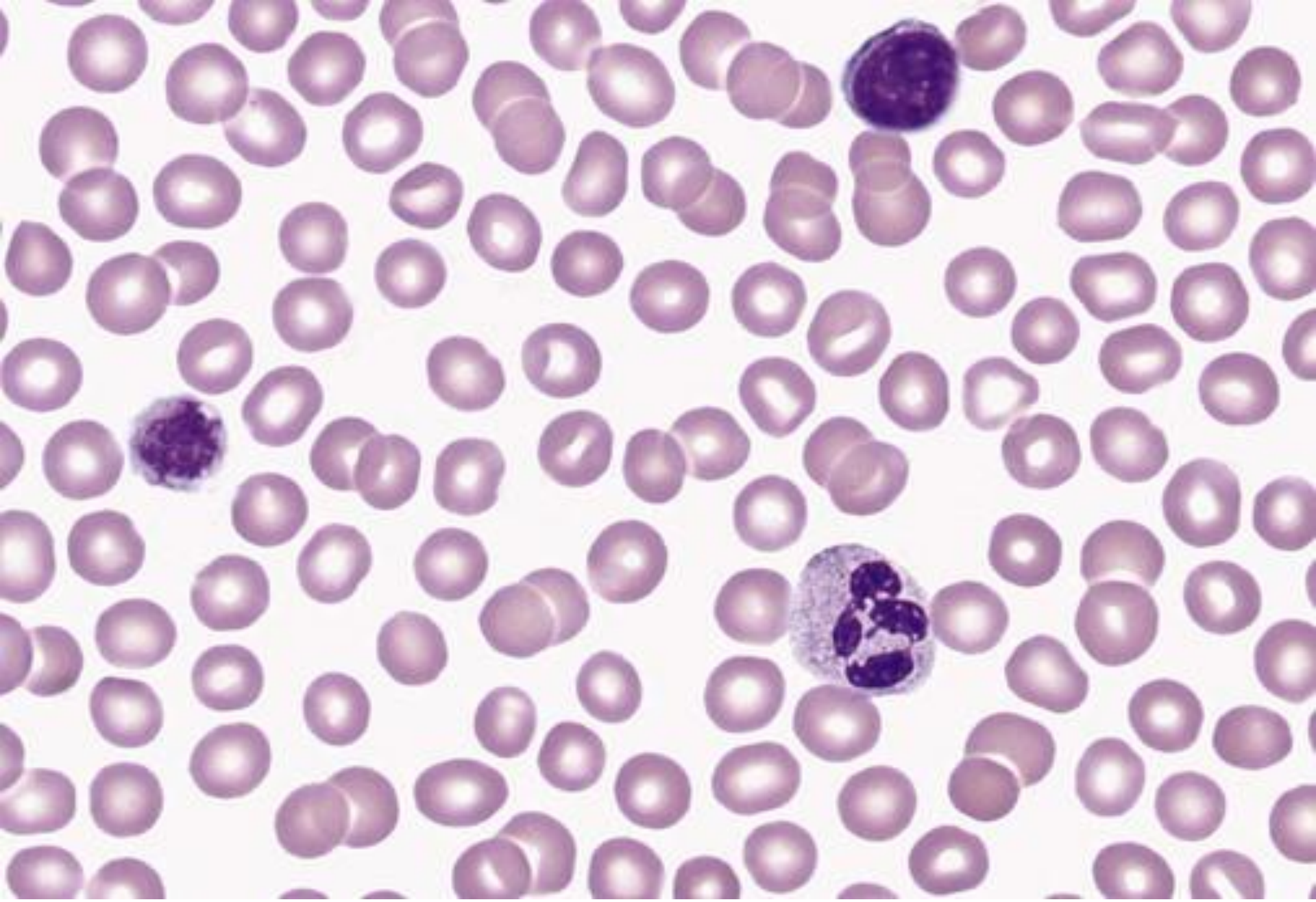
Investigations:

The diagnosis of ITP is partly made by exclusion. Fever, organomegaly, pancytopenia, lymphadenopathy, or abnormal peripheral blood cells should prompt an evaluation for malignant disease, such as leukemia, other bone marrow disorders.

- The blood smear is normal, apart from a greatly reduced platelet number, but no other abnormal cells such as blasts, which would accompany leukemia.
- The bone marrow demonstrates an obvious increase in megakaryocytes.
- Autoantibody testing performed if a diagnosis of connective tissue disease is likely.
- HIV testing should be considered.



Adequate platelet count in normal blood smear



ITP: Review of the peripheral smear reveals a paucity of platelets

Management

- Stable compensated ITP and a platelet count of more than 30×10^9/L do not require treatment to raise the platelet count, except at times of increased bleeding risk, such as surgery and biopsy.
- First-line therapy for patients with spontaneous bleeding is with prednisolone 1 mg/kg daily to suppress antibody production and inhibit phagocytosis of sensitised platelets by reticuloendothelial cells.
- Administration of intravenous immunoglobulin (IVIg) can raise the platelet count by blocking antibody receptors on reticuloendothelial cells, and is combined with corticosteroid therapy if there is severe haemostatic failure or a slow response to steroids alone.
- Life threatening bleeding should be treated with platelet transfusion in addition to the other therapies

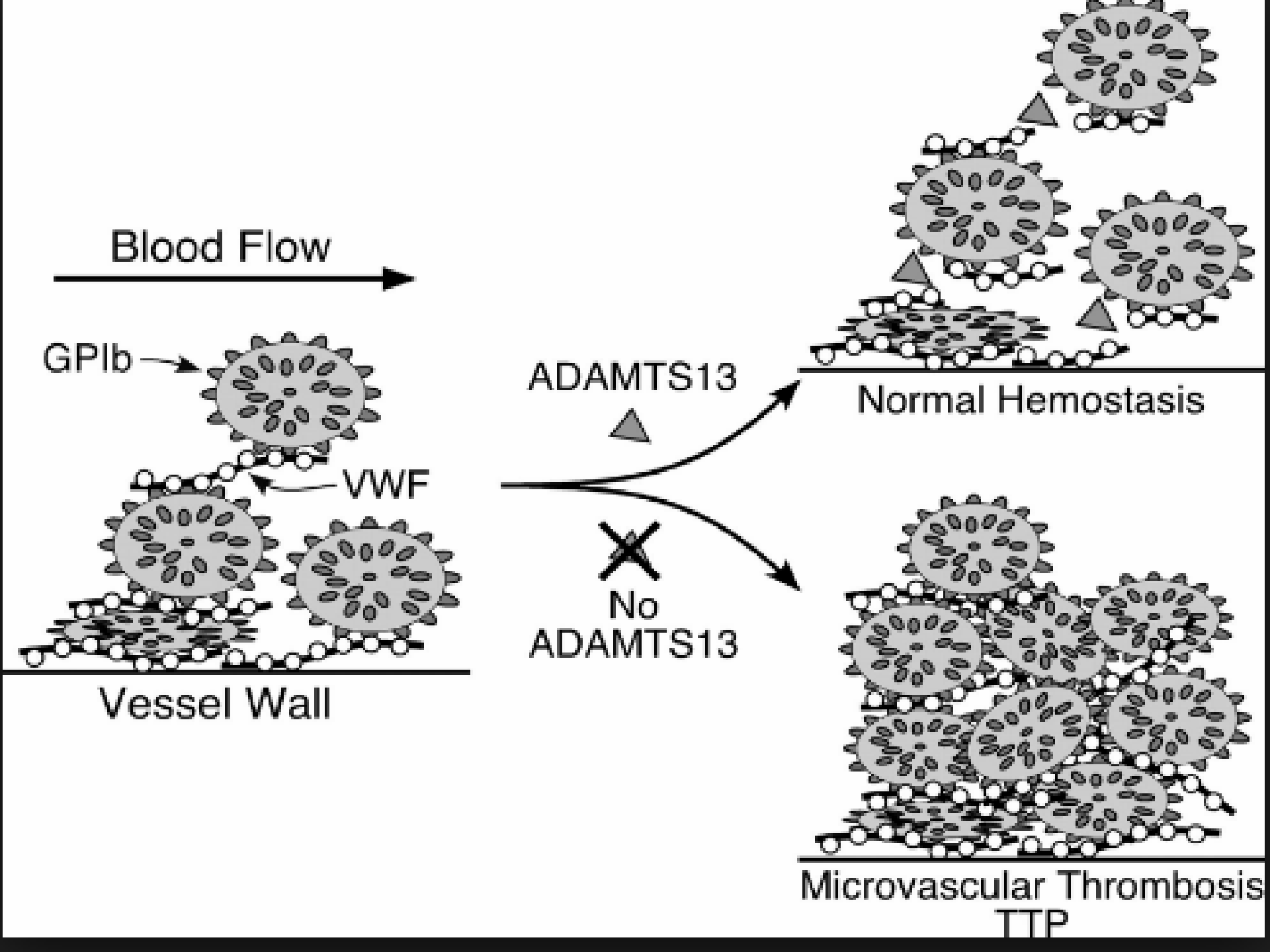
- Relapses should be treated by re-introducing glucocorticoids.
- If a patient has two relapses or primary refractory disease, second-line therapies are considered, which include the thrombopoietin receptor agonists eltrombopag and romiplostim, splenectomy and immunosuppression.
- Low-dose corticosteroid therapy, immunosuppressants such as rituximab, ciclosporin and tacrolimus should be considered in cases where the approaches above are ineffective.

Thrombotic thrombocytopenic purpura (TTP)

TTP is a disorder in which thrombosis is accompanied by paradoxical thrombocytopenia. TTP is characterized by a pentad of findings, although few patients have all five components:

1. Thrombocytopenia
2. Microangiopathic haemolytic anaemia
3. Neurological sequelae
4. Fever
5. Renal impairment

It is an acute autoimmune disorder mediated by antibodies against ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type-1 motif).


Blood Flow
GPIb
VWF
Vessel Wall
ADAMTS13
No
ADAMTS13
Normal Hemostasis
Microvascular Thrombosis
TTP

This enzyme normally cleaves vWF multimers to produce normal functional units, and its deficiency results in large vWF multimers which cross-link platelets.

The features are of microvascular occlusion by platelet thrombi affecting key organs, principally brain and kidneys.

It is a rare disorder (1 in 750 000 per annum), which may occur alone or in association with drugs (ticlopidine, ciclosporin), HIV, shiga toxins and malignancy.

It should be treated by emergency plasma exchange. Corticosteroids, aspirin and rituximab also have a role in management. Untreated mortality rates are 90% in the first 10 days, and even with appropriate therapy, the mortality rate is 20–30% at 6 months.

Heparin-induced thrombocytopenia (HIT)

HIT is a rare complication of heparin therapy, caused by induction of anti-heparin/PF4 antibodies which bind to and activate platelets via an Fc receptor.

This results in platelet activation and a prothrombotic state, with a paradoxical thrombocytopenia. HIT is more common with use of UFH rather than LMWH, and with higher doses of heparin.

Clinical features

Patients present, typically 5–14 days after starting heparin treatment. They may be asymptomatic, or develop venous or arterial thrombosis and skin lesions, including overt skin necrosis.

Diagnosis is by using the 4Ts scoring system:

1. The thrombocytopenia
2. The timing of the fall in platelet count
3. The presence of new thrombosis
4. The likelihood of another cause for the thrombocytopenia.

Management

Heparin should be discontinued as soon as HIT is diagnosed and an alternative anticoagulant which does not cross-react with the antibody substituted. Argatroban (a direct thrombin inhibitor) and danaparoid (a heparin analogue)

Disseminated intravascular coagulation (DIC)

DIC is a life-threatening nonimmune platelet destruction, characterised by systemic activation of the pathways involved in coagulation and its regulation. This may result in the generation of intravascular fibrin clots causing multiorgan failure, with simultaneous coagulation factor and platelet consumption causing bleeding. This triggered by endotoxin release or by severe tissue damage.

There is consumption of platelets, coagulation factors (notably factors V and VIII) and fibrinogen. The lysis of fibrin clot results in production of fibrin degradation products (FDPs), including D-dimers.

24.70 Disseminated intravascular coagulation

Underlying conditions

- Infection/sepsis
- Trauma
- Obstetric, e.g. amniotic fluid embolism, placental abruption, pre-eclampsia
- Severe liver failure
- Malignancy, e.g. solid tumours and leukaemias
- Tissue destruction, e.g. pancreatitis, burns
- Vascular abnormalities, e.g. vascular aneurysms, liver haemangiomas
- Toxic/immunological, e.g. ABO incompatibility, snake bites, recreational drugs

ISTH scoring system for diagnosis of DIC	
Presence of an associated disorder	Essential
Platelets	> 100 = 0 < 100 = 1 < 50 = 2
Elevated fibrin degradation products	No increase = 0 Moderate = 2 Strong = 3
Prolonged prothrombin time	< 3 sec = 0 > 3 sec but < 6 sec = 1 > 6 sec = 2
Fibrinogen	> 1 g/L = 0 < 1 g/L = 1

Total score

≥ 5 = Compatible with overt DIC

< 5 = Repeat monitoring over 1–2 days

(ISTH = International Society for Thrombosis and Haemostasis)

Management of DIC:

- Treat the underlying cause.
- Admission to intensive care to deal with concomitant issues, such as acidosis, dehydration, renal failure and hypoxia.
- Blood component therapy, such as fresh frozen plasma, cryoprecipitate and platelets, should be given if the patient is bleeding
- Established thrombosis should be treated cautiously with therapeutic doses of unfractionated heparin, unless clearly contraindicated.

Platelet function disorders

Causes

A- Acquired platelet function abnormalities

1- Drugs: The most common acquired disorders are iatrogenic, resulting from the use of aspirin, clopidogrel, dipyridamole and the GP IIb/IIIa inhibitors to prevent arterial thrombosis.

Modes of action of antiplatelet drugs:

Mode of action	Drug
Antiplatelet drugs	
Cyclo-oxygenase (COX) inhibition	Aspirin
Adenosine diphosphate (ADP) receptor inhibition	Clopidogrel Prasugrel Ticagrelor
Glycoprotein IIb/IIIa inhibition	Abciximab Tirofiban Eptifibatide
Phosphodiesterase inhibition	Dipyridamole

2- Uremic platelet dysfunction is caused by toxic proteins that accumulate in renal failure that inhibits platelet function. Control of uremic bleeding by:

1. **Dialysis**
2. **Maintenance of the hematocrit**
3. **DDAVP and cryoprecipitate, which has been shown to shorten the bleeding time significantly.**
4. **Conjugated estrogens are of some benefit for long-term treatment.**
5. **Platelet transfusions may be useful in patients with life threatening bleeding.**

B- Inherited platelet function abnormalities are relatively rare

1- Deficiency of the membrane glycoproteins, e.g. Bernard-Soulier syndrome and Glanzmann thrombasthenia.

Bernard-Soulier syndrome is caused by decreased surface expression of platelet GPIb (the primary von Willebrand factor) characterized by mild thrombocytopenia, increased bleeding time, and mild-to moderate bleeding symptoms.

Glanzmann thrombasthenia is characterized by an increased bleeding time and abnormally low levels of expression of platelet GPIIb/IIIa (the receptor for both vWF and fibrinogen) is an autosomal recessive condition associated with a variable but often severe bleeding disorder.

2- Defective plateletn granules, e.g. a deficiency of dense (delta) granules, giving rise to storage pool disorders

3- Congenital macrothrombocytopathies that are due to mutations in the myosin heavy chain gene MYH-9 are characterised by large platelets, inclusion bodies in the neutrophils (Döhle bodies) and a variety of other features, including sensorineural deafness and renal abnormalities.

Thrombocytosis (high platelet count)

24.15 Causes of a raised platelet count

Reactive thrombocytosis

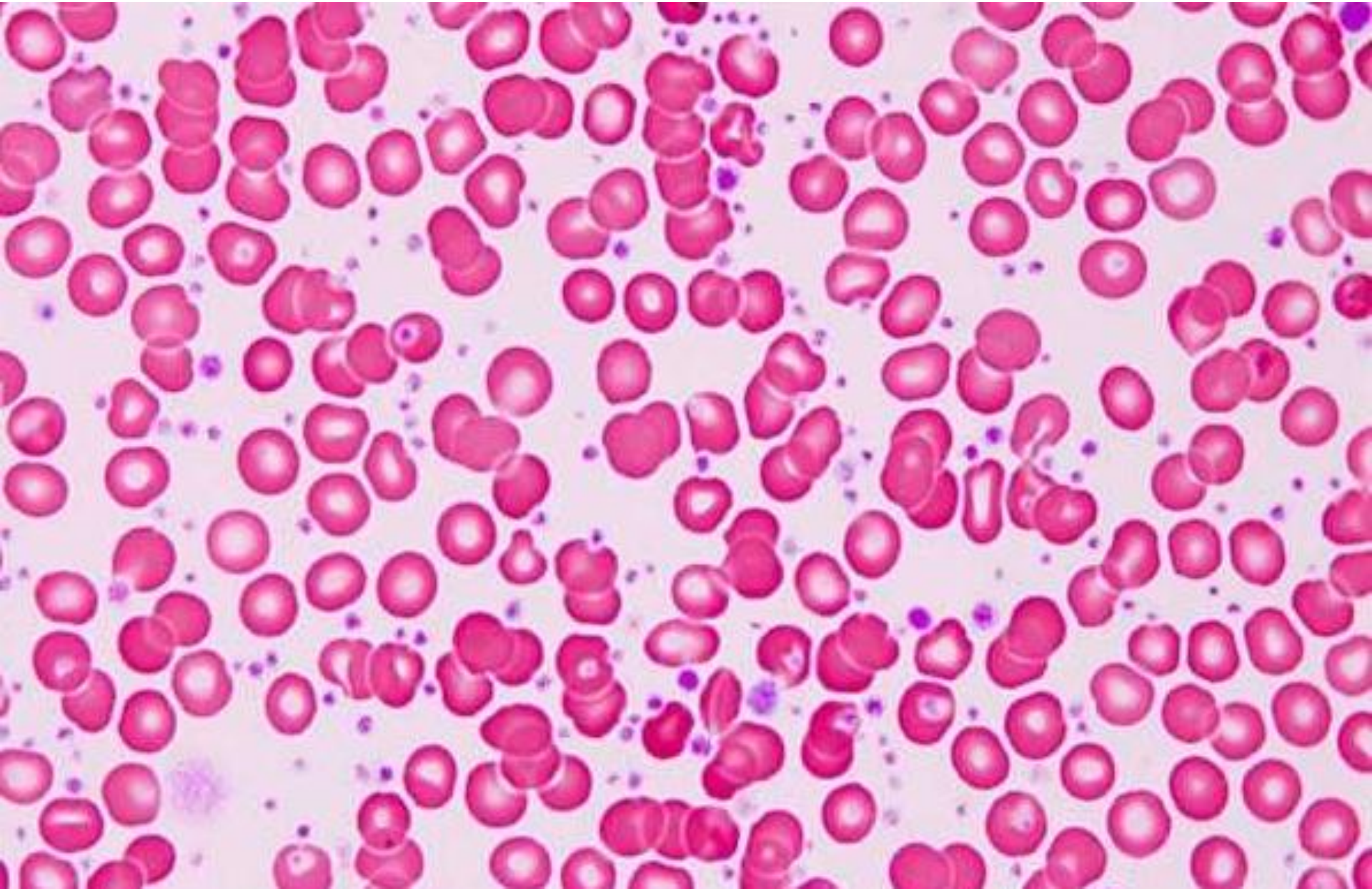
- Chronic inflammatory disorders
- Malignant disease
- Tissue damage
- Haemolytic anaemias
- Post-splenectomy
- Post-haemorrhage

Clonal thrombocytosis

- Primary thrombocythaemia
- PRV
- Chronic myeloid leukaemia
- Myelofibrosis
- Myelodysplastic syndromes (RARS with thrombocytosis, 5 q⁻ syndrome)

(PRV = polycythaemia rubra vera; RARS = refractory anaemia with sideroblasts)

- Is the presence of high platelet counts in the blood , it mean more than 450,000 per mm^3 (or microlitre) (or 450 x 10^9/L)
- The most common reason for a raised platelet count is that it is reactive to another process such as infection, connective tissue disease, malignancy, iron deficiency, acute haemolysis or gastrointestinal bleeding
- Patients with PRV, essential thrombocythaemia and occasionally myelofibrosis may present with thrombosis. Stroke and transient ischaemic attacks, amaurosis fugax, and digital ischaemia or gangrene are also features. In addition, to itching after exposure to water (aquagenic pruritus), splenomegaly and systemic upset. Platelet counts greater than 1,000,000/mcL are thought to increase the risk for thrombosis. Aspirin is indicated only in patients with symptomatic thrombosis. Concomitant therapy to prevent thrombotic complications of thrombocytosis includes lowering the platelet count with hydroxyurea.

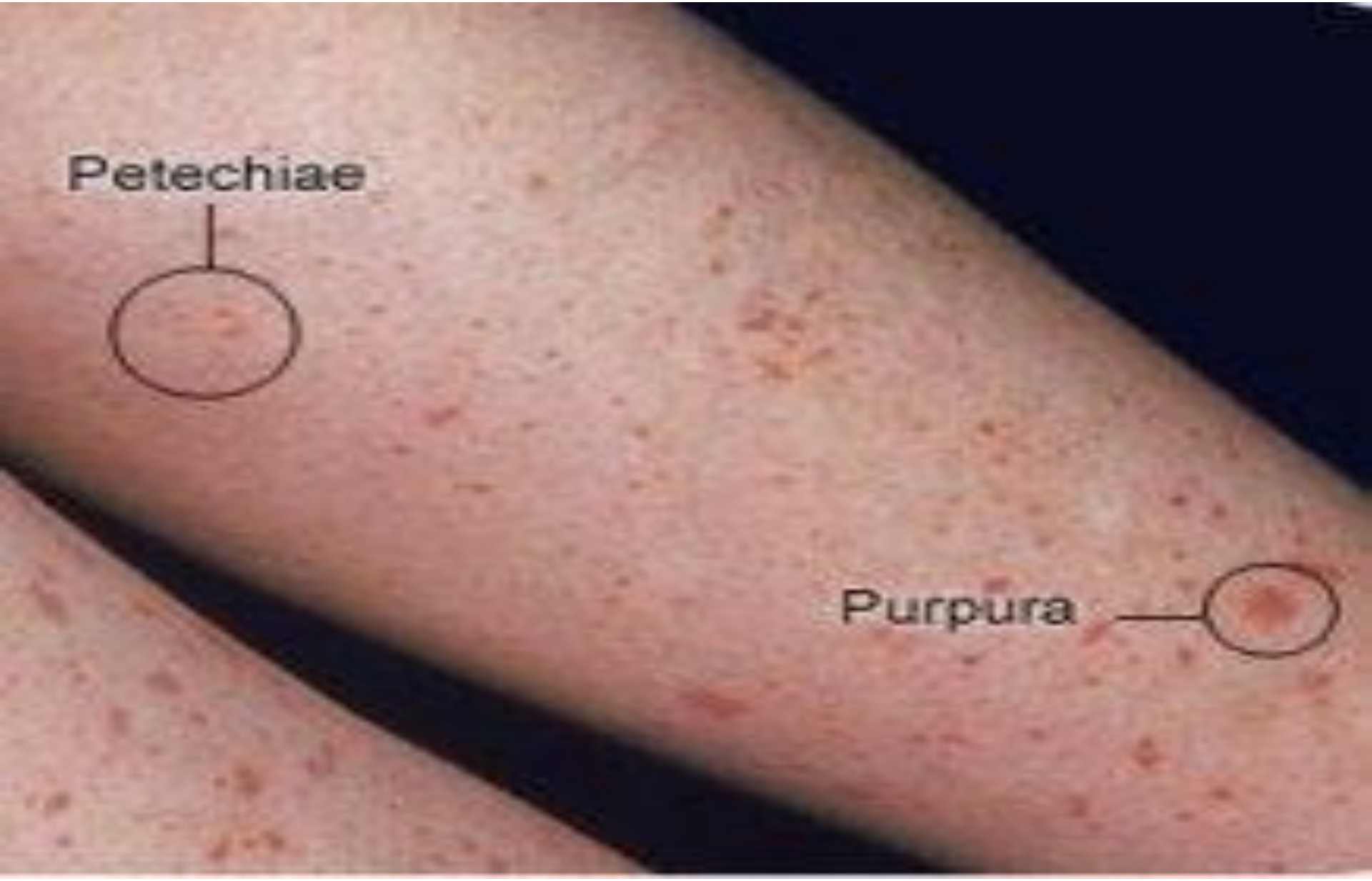


Peripheral blood smear in essential thrombocytosis showing increased platelet numbers.

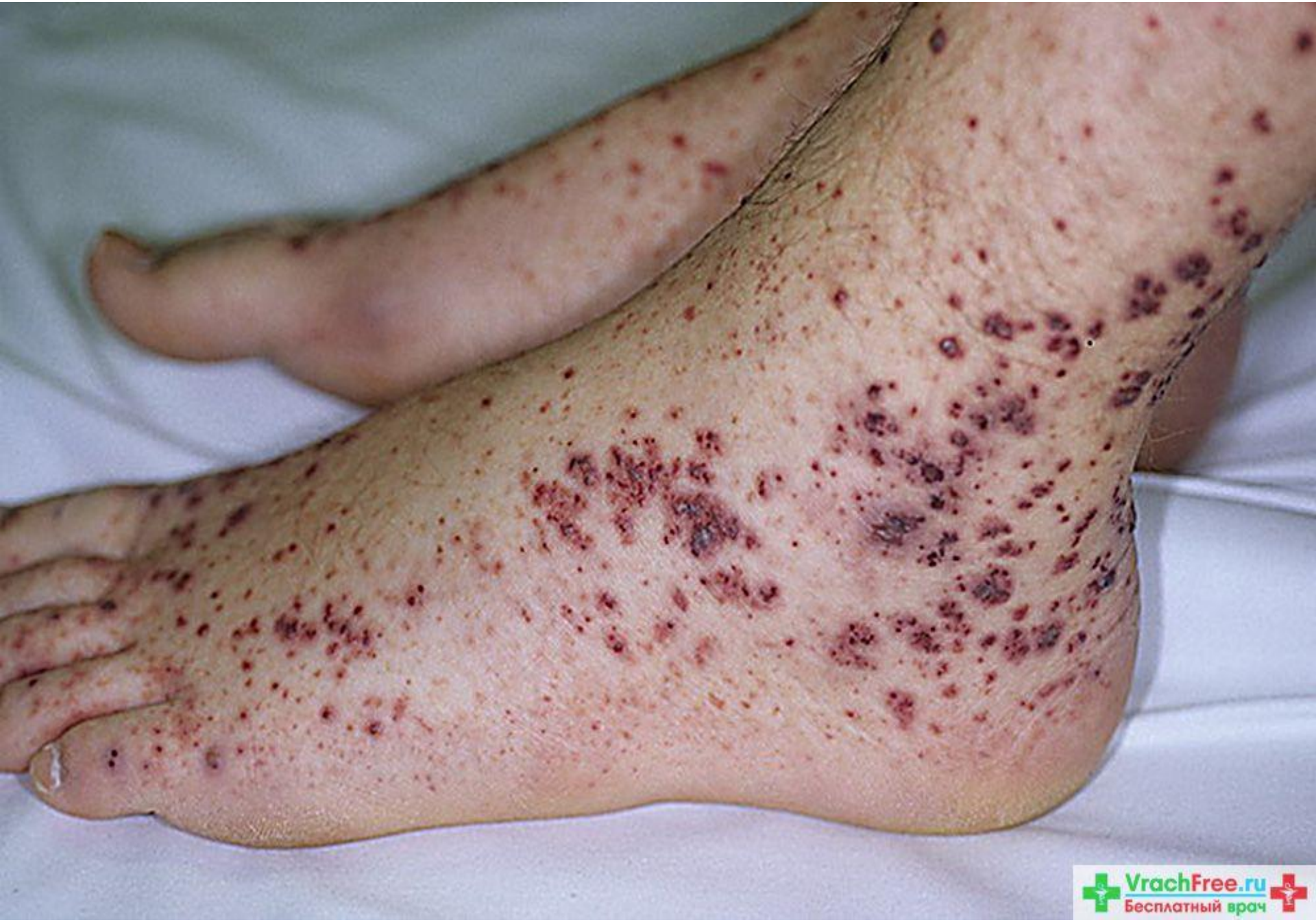
Causes of non-thrombocytopenic purpura

1. Senile purpura
2. Factitious purpura
3. Henoch- Schönlein purpura
4. Vasculitis
5. Paraproteinaemias
6. Purpura fulminans, e.g. in DIC secondary to sepsis

Petechiae / purpura is minor bleeding into the dermis that is flat and non-blanching. Petechiae are typically found in patients with thrombocytopenia or platelet dysfunction. Palpable purpura occurs in vasculitis.



Pinpoint red spots on the skin, called petechiae with larger purplish areas (purpura) caused by bleeding under the skin in patient with ITP



Vasculitis , Henoch - Schonlein purpura

Thanks