Doctor 22

PATHOLOGY

Sheet no. 2

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ACUTE INFLAMMATION

A. Normal: in general, we have equilibrium between hydrostatic pressure and colloid osmotic pressure.

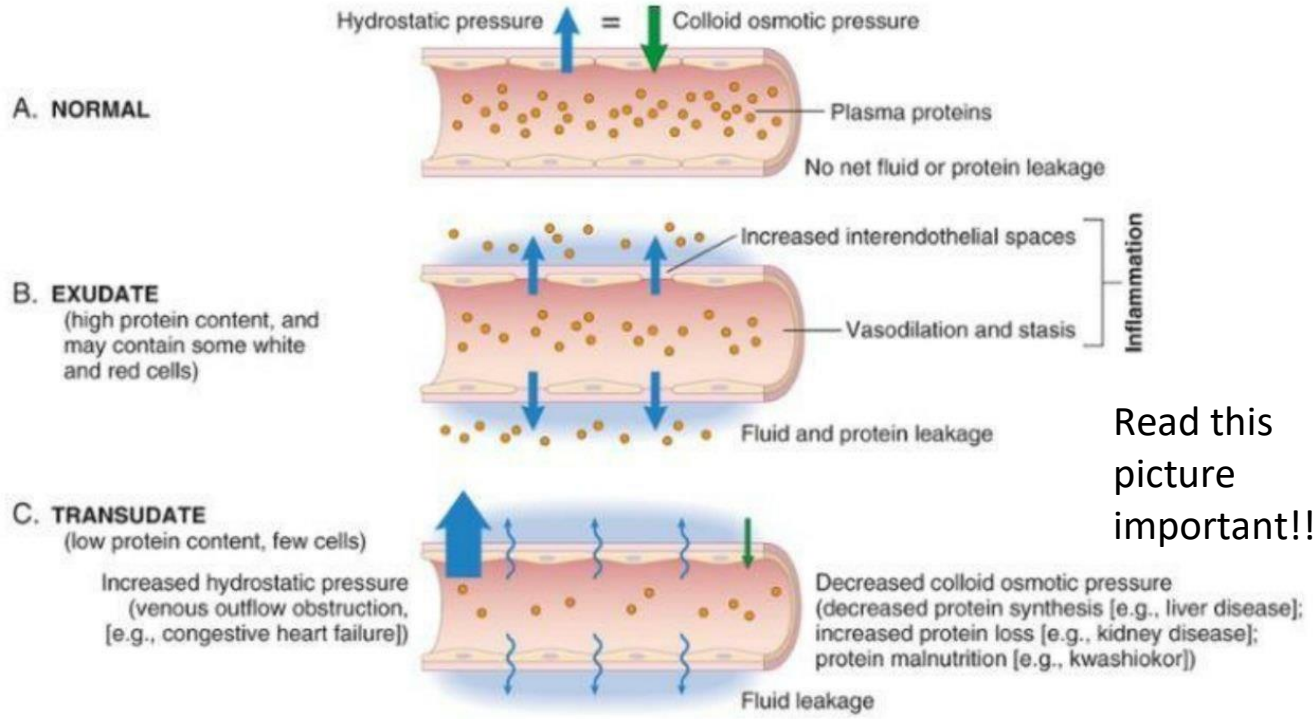
- Hydrostatic pressure: depends on the fluid volume inside B.V, as the fluid increases the pressure that moves the fluid outside increases too.
- Colloid osmotic pressure (oncotic pressure): depends on the concentration of proteins inside B.V, as the concentration increases the fluid retention increases.

Any change in equilibrium under certain conditions will lead to Exudate or Transudate.

B. Exudate: Fluid rich in proteins, cells, and debris which leaves the B.V.

C. Transudate: is mainly fluids that have low protein content and few cells which leaves the B.V.

We divide those into two different major components (exudate and transudate) because the pathogenesis in pathology that is associated with Exudate is different from the pathogenesis which is associated with Transudate. And the etiology is different as well.



Read this picture important!!

FIG. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue …*

Transudate	Exudate
Low protein	High protein
Low cell content	Many cells & debris
Low specific gravity	Higher specific gravity
Caused by osmotic/hydrostatic pressure imbalance	Caused by increased vascular permeability and denotes inflammatory reaction

Decrease in or Increase in

Very strong

EDEMA AND PUS:

Edema: excess fluids in interstitial or serous cavities (either transudate or Exudate).

Serous cavities like Pleural cavities, Peritoneal cavity, Pericardial cavity. Read about serous cavities from ChatGPT or google (:

As we said before, if these are caused by Exudate I must think about specific pathologies, if it is transudate I must think about different pathologies.

Pus (القيح): purulent exudate; inflammatory exudate rich in WBCs, debris, and microbes.

https://www.google.com/search?q=%D9%85%D8%A7+%D9%87%D9%88+%D8%A7%D9%84%D9%82%D9%8A%D8%AD

It indicates purulent inflammation: severe acute inflammation.

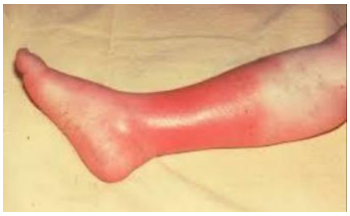
Whenever pus comes out from a cavity, we call it an abscess (دمل). Which is always an Exudate.

VASCULAR CHANGES (EARLY EVENTS)

Each step in inflammation has a mediator which causes it:

- **Vasodilatation: Histamine (the major responsible mediator for the initial phase of the inflammation) increases blood flow causing redness (erythema) and heat.**

Some people say that the first initial vascular response is an initial transient vasoconstriction. But it is so fast (seconds) and then go away so we don't consider it as first step.



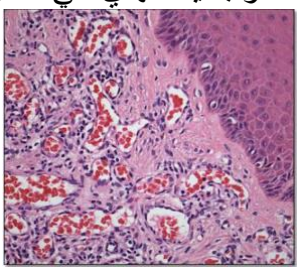
Abnormal

Hyperemia

- **Followed by increased permeability (exudate)**
- **Stasis; congestion and erythema.**

الدكتور ضرب مثال عن ال stasis ففرضا شارع الجامعة هو ال B.V وكان في اشي مسكر الطريق فالسيارات بتكون واقفة او بطيئة فهاي هي ال stasis. بتقدر برضه تقرأ عنها ب ChatGPT.

- **PMNs (Polymorphonuclear leukocytes) accumulate and adhere to endothelium then migrate outside the vessel into the interstitial.**



hyperemia الي بالصورة بتفسر ال blood cells كمية ال

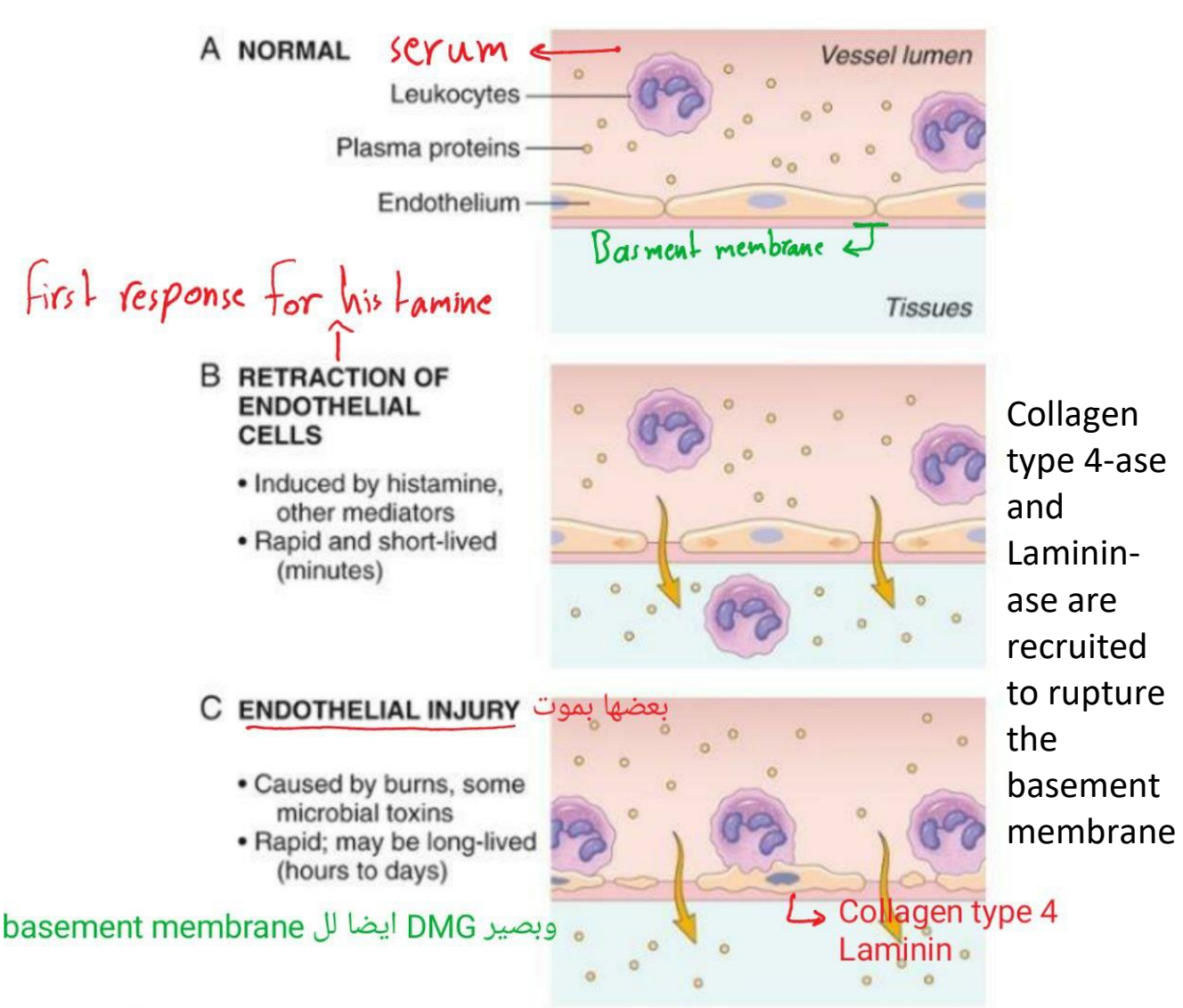


FIG. 3.3 Principal mechanisms of increased vascular permeability in inflammation and ...

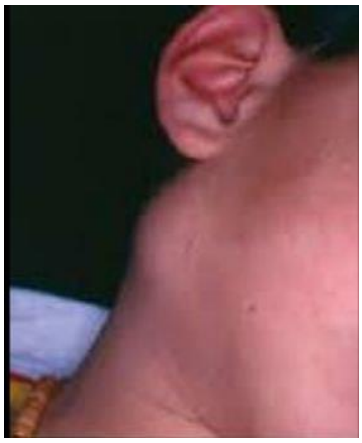
Collagen type 4-ase and Laminin-ase are recruited to rupture the basement membrane

this is how the histamine and initial vascular dilators increase the vascular permeability.

LYMPHATIC VESSELS AND LYMPH NODES:

Lymphatic vessels: they are vascular channels which drain the interstitial fluid into the lymph nodes.

- **Lymphangitis: inflammation and proliferation of lymphatic vessels to drain fluids and other elements.**
- **Drainage to nearby lymph nodes; hence causing lymphadenitis, which could either be reactive lymphadenitis (majority) or inflammatory lymphadenitis.**



Summary

Vascular Reactions in Acute Inflammation

- Vasodilation is induced by inflammatory mediators such as histamine (described later), and is the cause of erythema and stasis of blood flow.
- Increased vascular permeability is induced by histamine, kinins, and other mediators that produce gaps between endothelial cells, by direct or leukocyte-induced endothelial injury, and by increased passage of fluids through the endothelium.
- Increased vascular permeability allows plasma proteins and leukocytes, the mediators of host defense, to enter sites of infection or tissue damage. Fluid leak from blood vessels (exudation) results in edema.
- Lymphatic vessels and lymph nodes also are involved in inflammation, and often show redness and swelling.

LEUKOCYTES ROLE:

Our WBCS are called Leukocytes. Leuko which means "White", Cytes means "Cells". They are a major component of our inflammatory cells. Now the two major inflammatory cells that play important roles are:

- PMNs: polymorph-nuclear cells or neutrophil, multi nuclear-granulated cells.
- Macrophages: or tissue macrophages, when they are circulating in the blood they are called monocytes, and they are mono nuclear white blood cells.

How do they play roles during an injury? Specific mediators call/recruit them to the injured tissue from the intravascular compartment to the site of injury.

Migration of leukocytes from BV to tissue is multistep process: adhesions, then transmigration, then movement toward the enemy area.

Both neutrophil and macrophages have the capacity to eliminate the enemy via phagocytosis. (بلعمة الجسم الغريب)

The table below shows the properties of both neutrophils and macrophages. The doctor said it's very important and not to worry, we will memorize it step by step. But let's take some quick notes: ☺

- Neutrophils have a relatively short life span. However, later we will learn the roles for the dead ones.
- When macrophages are circulating in the bloodstream, they are called monocytes, once they leave the blood vessels, they are called tissue macrophages and their life spans become elongated.

More table information will be discussed later/when the course progresses

HSCs means hematopoietic stem cells which are cells that reside primarily within bone marrow during adulthood.

TABLE 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil extracellular traps.
This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

ADHESION (WBCS TO ENDOTHELIUM)

We talked before about how the movement of the WBCs from the intravascular compartment to the interstitial compartment or the site of injury is a multistep process, so now we are going to talk about these steps:

1) Margination
2) Rolling
3) Adhering

Chemotaxis: is the movement of WBCs from intravascular compartment to the site of injury, and mainly macrophages and neutrophils.

Let's discuss the picture below to understand each step.

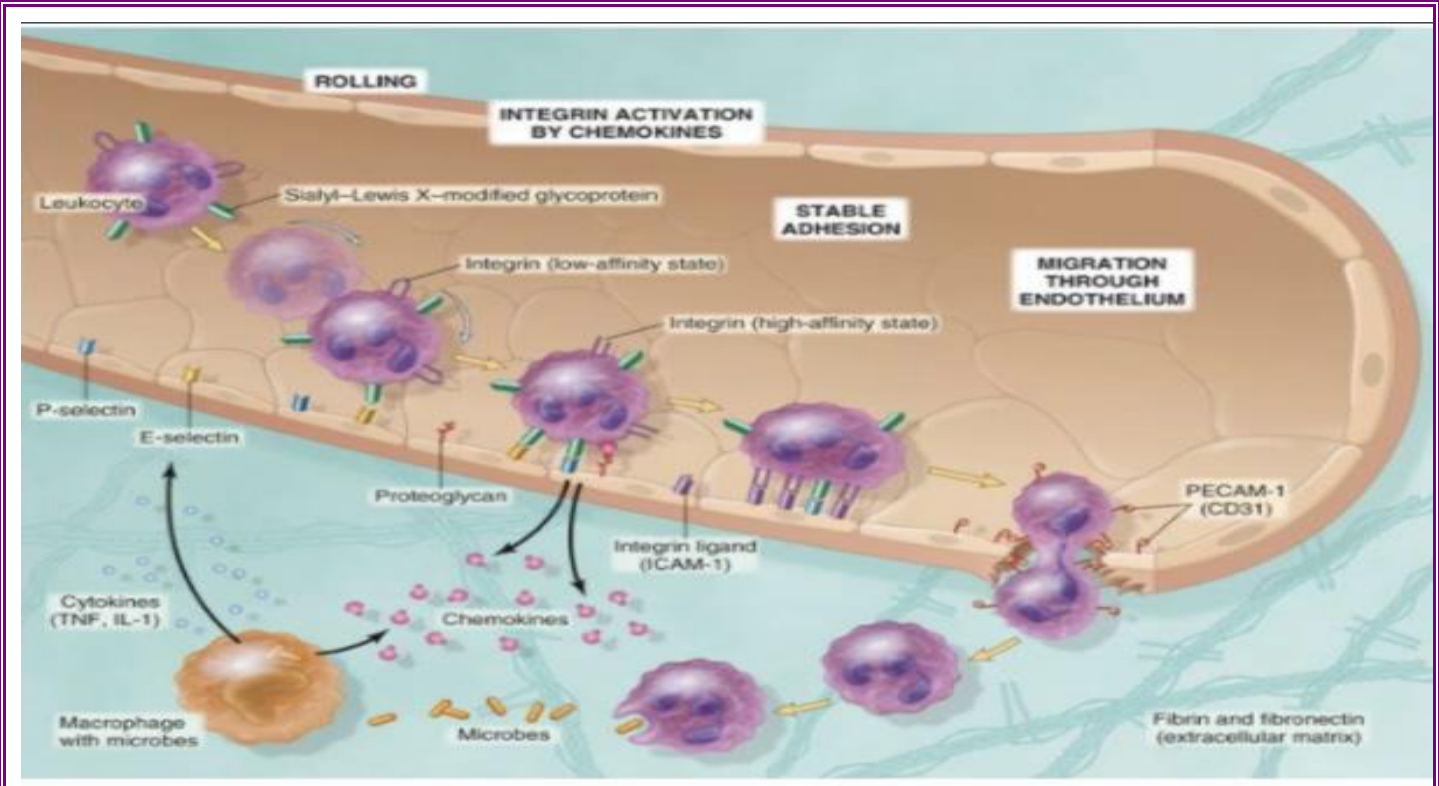


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he..

This is a longitudinal section of a blood vessel. First question to ask is "What is the cell shown in the picture?" Well, because it is multi-nucleated and has receptors including integrins and selectins, it is a Neutrophil.

- The first step, which is Margination: is when the cells start to move from the central line of the lumen to the periphery line (يعني بتدحرج من وسط الوعاء الدموي للأطراف). Upon the secretion of proper inflammatory mediator chemotactic agents, these agents attract the cells to the periphery of the lumen (بتنادي عليهم). As we took in histology course, the cells are in the central 1/3 of the vessel so the movement of these cells from the central to the periphery called margination.

- The second step, which is Rolling: is the movement of the cells by specific mediators on the walls of the blood vessel

- The third step is Adhering: which starts with weak adhering (selectins) and then strong adherence (integrins)

Then there will be certain enzymes called PECAM-1 (CD31) and which are transmembrane receptors and proteins that exist in all cells and especially in inflammatory WBCs. These enzymes cut the basement membrane and endothelial cells to make road for WBCs to pass through.

How can the WBCs pass through? WBCs contain cytoplasmic filaments that allow it to fold and bend to fit through.

Some people/books called this transient exist of WBCs "Diapedesis", others called the entire chemotactic movement that as well.

The main driver for the vascular phase is Histamine. there are many others but histamine is the strongest, while in the animals is serotonin

Let's summarize the steps:

Margination —> Rolling—> weak adherence (selectins)—> strong adherence (integrin)—> Diapedesis (trans migration)

Those are the active steps and each one has its own mediators, but the most important one is the initial one histamine.

This table below is not for memorizing.

You just need to know that PECAM (CD31) is the major mediator that is responsible for the trans migration by secreting collagen type 4-ase and laminin-ase so the WBCs could exit.

TABLE 3.4 Endothelial and Leukocyte Adhesion Molecules

Family	Molecule	Distribution	Ligand
Selectin	L-selectin (CD62L)	Neutrophils, monocytes T cells (naïve and central memory) B cells (naïve)	Sialyl-Lewis X/PNAd on GlyCAM-1, CD34, MAdCAM-1, others; expressed on endothelium (HEV)
	E-selectin (CD62E)	Endothelium activated by cytokines (TNF, IL-1)	Sialyl-Lewis X (e.g., CLA) on glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
	P-selectin (CD62P)	Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin; platelets	Sialyl-Lewis X on PSGL-1 and other glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
Integrin	LFA-1 (CD11aCD18)	Neutrophils, monocytes, T cells (naïve, effector, memory)	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	MAC-1 (CD11bCD18)	Monocytes, DCs	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	VLA-4 (CD49aCD29)	Monocytes T cells (naïve, effector, memory)	VCAM-1 (CD106); expressed on endothelium (upregulated on activated endothelium)
	α4β7 (CD49DCD29)	Monocytes T cells (gut homing naïve effector, memory)	VCAM-1 (CD106), MAdCAM-1; expressed on endothelium in gut and gut-associated lymphoid tissues
Ig	CD31	Endothelial cells, leukocytes	CD31 (homotypic interaction)

CLA, Cutaneous lymphocyte antigen-1; *GlyCAM-1*, glycan-bearing cell adhesion molecule-1; *HEV*, high endothelial venule; *ICAM*, intercellular adhesion molecule; *Ig*, immunoglobulin; *IL-1*, interleukin-1; *MAdCAM-1*, mucosal adhesion cell adhesion molecule-1; *PSGL-1*, P-selectin glycoprotein ligand-1; *TNF*, tumor necrosis factor; *VCAM*, vascular cell adhesion molecule.

Read this summary to organize your information

Summary

Leukocyte Recruitment to Sites of Inflammation

- Leukocytes are recruited from the blood into the extravascular tissue where infectious pathogens or damaged tissues may be located, migrate to the site of infection or tissue injury, and are activated to perform their functions.
- Leukocyte recruitment is a multistep process consisting of loose attachment to and rolling on endothelium (mediated by selectins); firm attachment to endothelium (mediated by integrins); and migration through interendothelial gaps.
- Various cytokines promote the expression of selectins and integrin ligands on endothelium (TNF, IL-1), increase the avidity of integrins for their ligands (chemokines), and promote directional migration of leukocytes (also chemokines). Tissue macrophages and other cells responding to the pathogens or damaged tissues produce many of these cytokines.
- Neutrophils predominate in the early inflammatory infiltrate and are later replaced by monocytes and macrophages.

May all of you have the mistake-ase enzyme in the exam ;)

اللهم احرس أهل فلسطين بعينك التي لا تنام.
اللهم اجعل لأهل فلسطين النصرة والعزة والغلبة والقوة والهيبة.
اللهم انصر أهل فلسطين وثبت أقدامهم.