وزارة التعليم العالي والبحث العلمي
الجامعة التقنية الشمالية
اسم التشكيل :- المعهد التقني الدور

الحقيبة التعليمية

قسم تقنيات المختبرات الطبية

اسم المقرر:	Immunology and pathogenicity
المرحلة / المستوى:	Second
الفصل الدراسي:	Second
السنة الدراسية:	٢٠٢٥ / ٢٠٢٦

معلومات عامة

اسم المقرر:	Immunology and pathogenicity					
القسم:	Medical Laboratory Technologies					
الكلية: المعهد	Dour Technical Institute					
المرحلة / المستوى	Second					
الفصل الدراسي:	Second					
عدد الساعات الاسبوعية:	نظري	١	عملي	٢		
عدد الوحدات الدراسية:	٣					
الرمز:	MLT٢١٧					
نوع المادة	نظري		عملي		كلهما	*
هل يتوفر نظير للمقرر في الاقسام الاخرى	No					
اسم المقرر النظير	-					
القسم	-					
رمز المقرر النظير	-					

معلومات تدريسي المادة

اسم مدرس (مدرسي) المقرر:	Hanan Shihab Ahmed
اللقب العلمي:	Assistant Professor
سنة الحصول على اللقب	٢٠١٩
الشهادة :	Doctor
سنة الحصول على الشهادة	٢٠١٦
عدد سنوات الخبرة (تدريس)	١٤

الوصف العام للمقرر

يكتب في هذا الجزء وصفاً عاماً و ملخصاً للمقرر الدراسي :-

General understanding of the concept of immunological disorders and knowledge of the causes of immune diseases

١. اسم المقرر
Immunology and pathogenicity
٢. رمز المقرر
MLT٢١٧
٣. الفصل / المستوى
Second/ Second
٤. تأريخ اعداد الوصف
٢٠٢٤/٣/٧
٥. اشكال الحضور المتاحة
Weekly presence
٦. عدد الساعات الدراسية (الكلية) / عدد الوحدات (الكلية)
٣ / ٤٥
٧. اهداف المقرر

اهداف المقرر الدراسي	• The goal of the course is to make sense of the fundamental concepts and terminology of immunology while focusing on the vital components of natural immunity—chemical, biochemical, physiological, and cellular immunological barriers—and antivirals in particular. Focus on antivirals, as well as the different mechanisms taken by microorganisms to resist the immunity of the body and the different mechanisms to cause diseases.

٨. استراتيجيات التعليم والتعلم
• Explanation of the course • Daily exams • Student groups • Field visits

٩. بنية المقرر

weeks	times	Subject	Learning method	Attendance Forms	Method of examination
First	٣	Definition of immunity, Types, and its relationship to other natural and biological sciences	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Second	٣	Immune response, and types	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Third	٣	The biological processes linked to diseased states	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Fourth	٣	Immunization against viruses, and types - Specific immunity - Non-Specific immunity	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Fifth	٣	Immunization against bacteria, and types - Specific immunity - Non-Specific immunity	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Sixth	٣	Immunization against Parasities, and types - Specific immunity - Non-Specific immunity	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Seventh	٣	Immunization against fungi, and types - Specific immunity - Non-Specific immunity	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams

weeks	times	Subject	Learning method	Attendance Forms	Method of examination
Eighth	٣	Mechanisms of neutralization, of bacterial and fungal toxins	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Ninth	٣	Osmosis and phagocytosis	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Tenth	٣	Autoimmunity and theories of formation of various autoimmune diseases	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Eleventh	٣	Types of immune diseases - lupus erythematosus - Rheumatoid arthritis	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Twelve	٣	Mechanism of Rh factor in hemolysis at birth	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Thirteenth	٣	Hypersensitivity	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Fourteenth	٣	ELIZA test	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams
Fifteenth	٣	RIA test	Explain the lecture, PowerPoint presentations, and practical applied	Classroom and Laboratory	Exams

١٠. تقييم المقرر

Daily, monthly, and final exams, as well as weekly reports.

١١. مصادر التعلم والتدريس

scientific books

Main references for Immunology and pathogenicity

Scientific papers for immunology and pathogenicity

weeks	times	Subject	Learning method	Attendance Forms	Method of examination
Online scientific resources					

الاهداف العامة

١. Identify immune pathogens and their cells.
٢. Recognize special immunity diseases.
٣. Identify the methods by which immunological disorders can be identified.

الأهداف الخاصة

- Introduce the student to immunological disorders, the mechanisms that contribute to the pathophysiology of the body, the cells that make up the body's defensive mechanism, and the methods for diagnosing and treating these conditions.

أمثلة الأهداف التعليمية

الأهداف السلوكية او نواتج التعلم

١. **The learner has to be aware of the significance of immunity diseases and understand the components of the immune system.**
٢. **Distinguish between immunological diseases.**
٣. **The student must be able to carry out certain tests and diagnose immunological disorders.**

((Educational aims): After finishing the lesson (lecture), the learner will be able:-

١- Knows the immunity diseases.
٢- Know what types of immune diseases and distinguish between them.

المتطلبات السابقة

- اذكر أي متطلبات سابقة قد يحتاجها الطالب قبل التسجيل في المقرر، مثل مواد دراسية سابقة أو مهارات معينة.
- **Identify particular disorders that affect the immune system and how to detect and treat them.**

الأهداف السلوكية او مخرجات التعليم الأساسية		
ت	تفصيل الهدف السلوكي او مخرج التعليم	آلية التقييم
١	Student Understanding of Immunological Disorders.	• Lectures. • Home works and participation. • Discussions and tests.
٢	The student gets the ability to identify immunological types.	• Research and skill development through scientific reports
٣	Ability to provide immunology information, and diagnosis.	• Home works • Tests
٤	The student's understanding of the significance of immunity for the human body	• Home works • Tests

أساليب التدريس (حدد مجموعة متنوعة من أساليب التدريس لتناسب احتياجات الطلاب ومحتوى المقرر)

	مبررات الاختيار	الاسلوب او الطريقة
	Classical lectures	**١. Lectures and practical lectures**
	Interactive Lecture	**٢. Interactive and mutual learning**
	The skill of interpreting information	**٣. Learning via reasons and evidence**
	Provide abstract and understanding of the topic	**٤. Discussion at the finish of the lecture**

Theoretical syllabus	
Weeks	**Topics**
١-٢-٣	Gel-diffusion , ring test , tubes –test ١-single diffusion at one direct. ٢-double diffusion at one direct. ٣- Single diffusion at tow direct. ٤- Double diffusion at tow direct. ٥-electropheresis, their types. Student, homework (differences among ١,٢,٣,٤, and also between ٥, ٦ ,neutralization, definition. , types. A-viral neutral. e.g. (ASOT) opsonization test ١-direct-method ٢-Indirect method RIA ELIZA Analysis by strips.
٤,٥	Immune – response Humoral response Primary &secondary responses. Ab .production factors , Cellular response types Lymphokines types
	Micro organisms immunity A-immunity against bacteria following bacterial infection, role of every system (briefly) for arrest

٦,٧	of such infection. Types of cellular &humeral specific immunity. Types of their agents for each one. Role of Antibody for arrest of infect. ١-toxin – neutralization with examples. ٢-complement activation with examples. ٣-opsonization & phagocytosis.
٨	B- Immunity against viruses. ١-The specific immunity. ٢-non specific immunity, their type's examples on the tests in parasites diagnosis.
٩	c- Immunity against parasites examples on tests to parasites diagnosis. General idea about the humoral cellular immunity against the protozoa and against helminthes.
١٠	Immunity against fungi and that against parasites revision.
١١	Micro organism's immunity.
١٢	Auto immunity , theories of the formation of auto immune diseases Examples of AID with examples e.g. Rhematioud arthritis e.g. SLE , mechanism explanation Rh- factor in born hemolysis
١٣-١٤	Hyper sensitivity, definition. Examples with tables of each one I-types with illustrated diagram about occurring with examples about diseases cases (also the same with ٤ types) anaphylaxis mechanism. Concentrate on the subject connected with diseases of serologic &immunologic tests in the lab.

١٥	AIDS & immunity .the disease and its relation with the immune system. ELIZA

خارطة القياس المعتمدة

المحتوى التعليمي	عناوين الفصول	الأهمية النسبية	الأهداف السلوكية					عدد الفقرات
			المعرفة	الفهم	التطبيق	التحليل	التقييم	
الفصل الثاني / المستوى الثاني	المناعة والامراضية	٪١٠٠	٪٣٥	٪١٠	%٢٥	٪١٠	٪٢٠	٥
الفصل الثاني/ المستوى الثاني	انواع الامراض المناعية واسبابها وتشخيصها	٪١٠٠	٪٣٥	٪١٠	٪٢٥	٪١٠	٪٢٠	٥

الاسبوع الاول والثاني والثالث

أ.الفئة المستهدفة Target Population

طلبة المرحلة الثانية-قسم المختبرات الطبية

المحتوى

- **Immunodiffusion**
- **Types of precipitation Method**
- **Used Medium**
- **Lmmunoelectrophoresis**
- **ELISA**
- **The immune response to infection**

▶ الاختبار القبلي (Pre-Test)

Q١/ What are difine of Immunodiffusion

Q٢/ What are commonly types

Immunodiffusion is a diagnostic test which involves diffusion through a substance such as agar which is generally soft gel agar (٢٪) or agarose (٢٪), used for the detection of antibodies or antigen.

The commonly known types are:

١. Single diffusion in one dimension (Oudin procedure)

٢. Double diffusion in one dimension (Oakley Fulthorpe procedure)

٣. Single diffusion in two dimensions (radial immunodiffusion or Mancini method) Double diffusion in two dimensions (Ouchterlony double immunodiffusion)

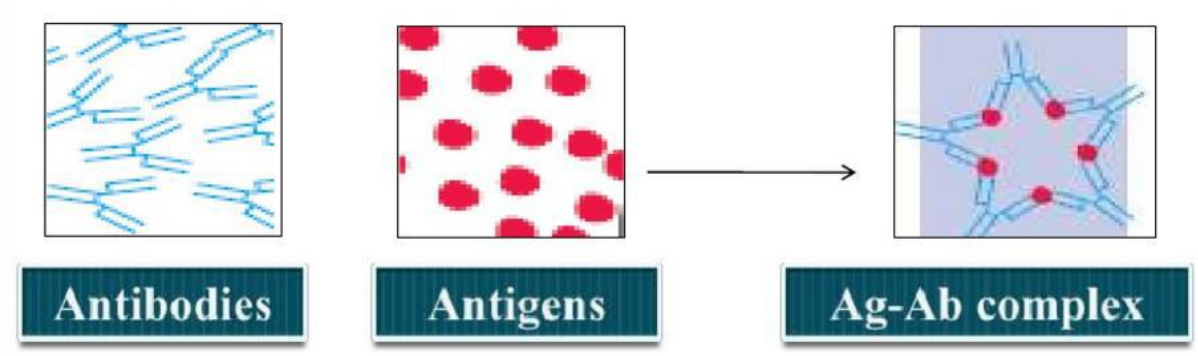
Types of precipitation Method

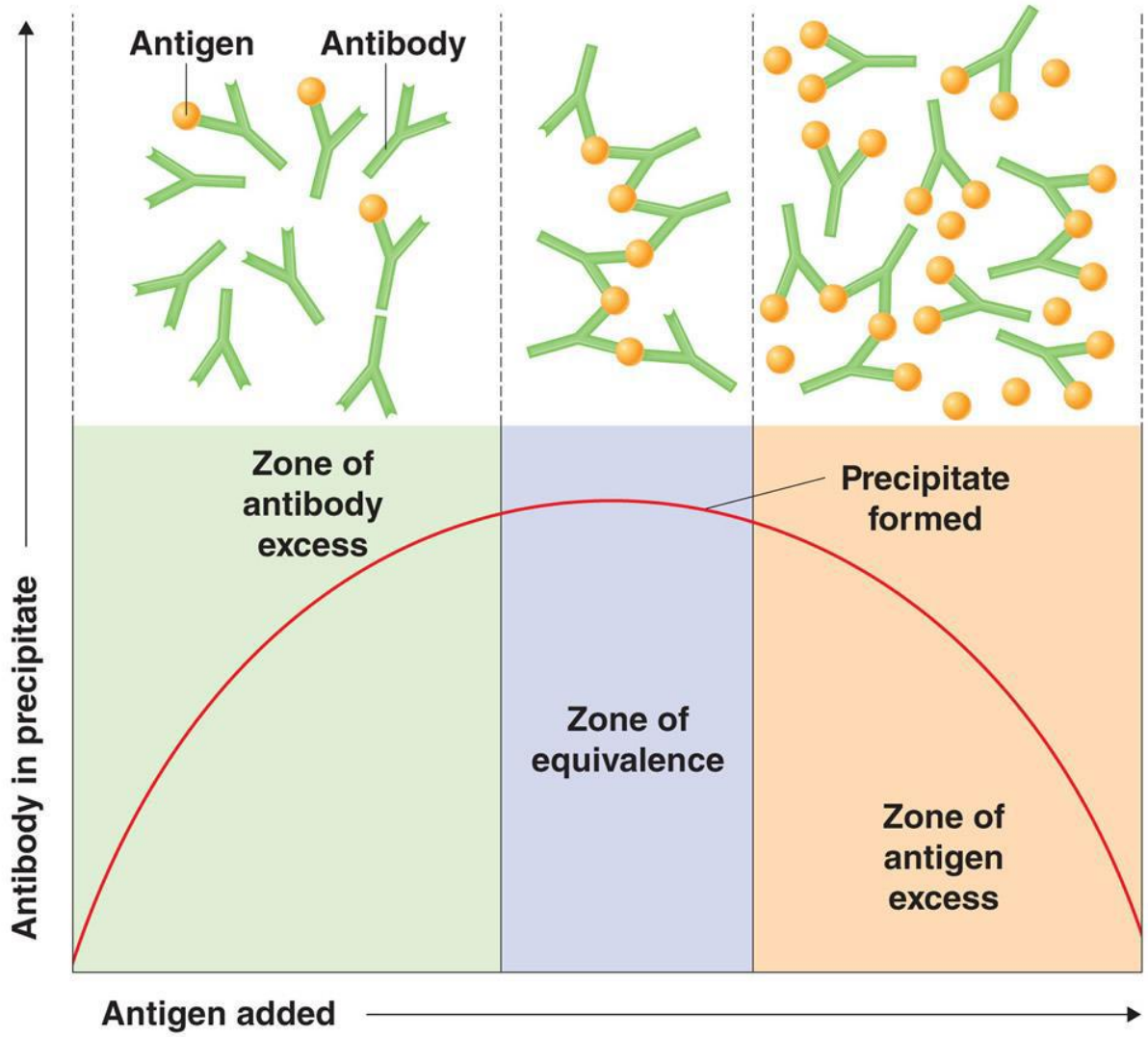
Singlediffusion(Radialimmunodiffusion).

•Doublediffusion(Ouchterlony).

•Immunoelectrophoresis.

•Immunofixation.





Used Medium

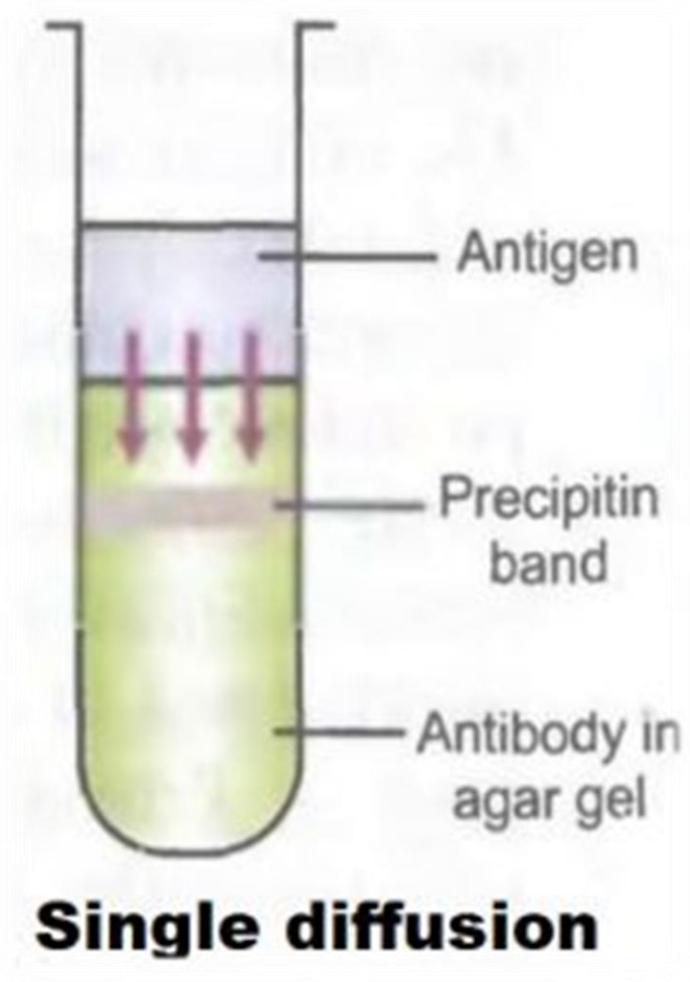
١.Agar contain high molecular weight complex of polysaccharide, addition of ٠.٣- ١,٥٪ agar will diffuse most of reactants

-Agar has strong negative charge

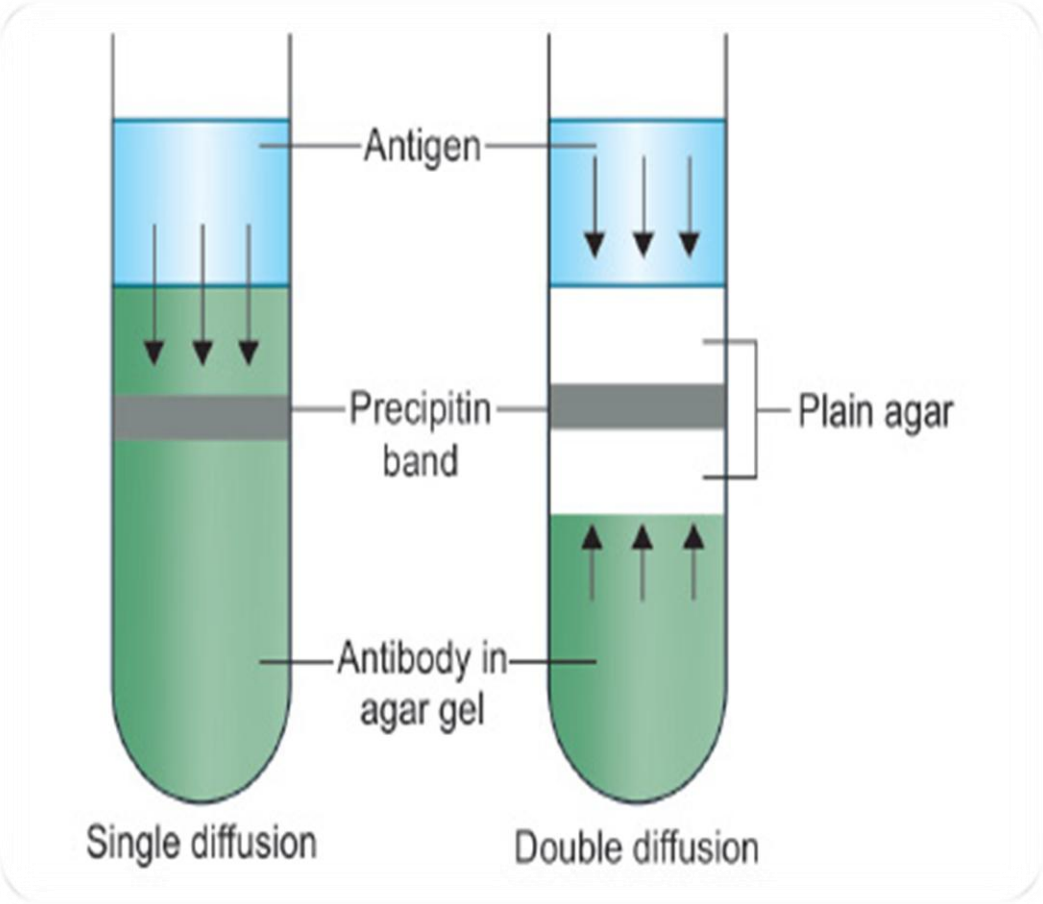
٢.Agarose purified agar used to help stabilize the diffusion process and allow visualization of precipitation bands

A- Single Diffusion in One Dimension

- In this test, the antibody is incorporated in agar gel and the antigen solution is layered over it
- The antigen diffuses downward, reacts with antibody and forms precipitation band.
- The number of bands indicates the number of Ags in a mixture



- B- Double Diffusion in One Dimension
  In this test, both Ag and Ab move towards each other by diffusion
- The Ab incorporated in agar gel is placed at the bottom of tube
- Above this, a column of **plain agar is added**
- On the top of column of plain agar Ag solution is layered
- Ag and Ab move towards each other through the
- column of plain agar and form a band of precipitate

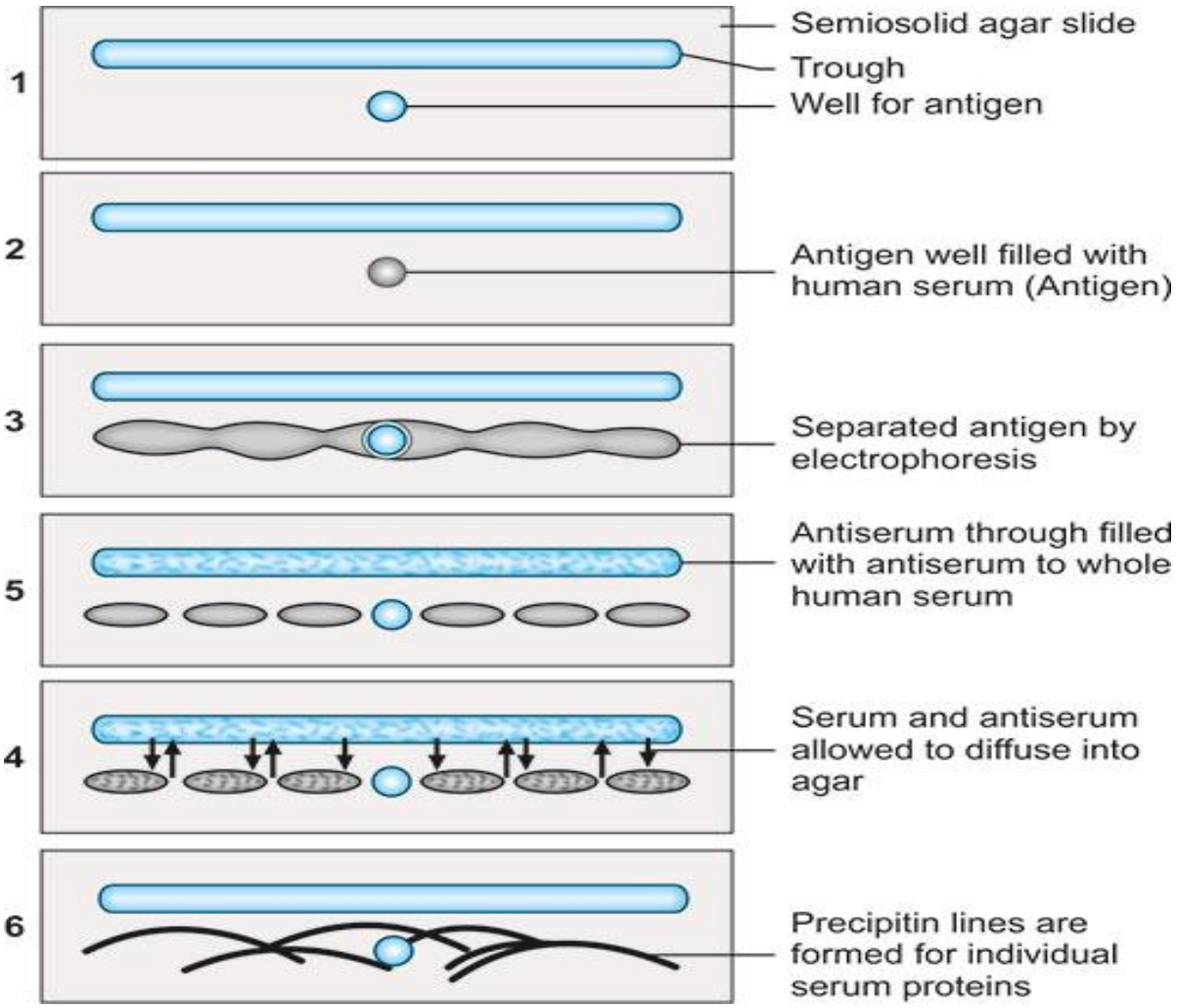

Antigen
Precipitin band
Plain agar
Antibody in agar gel
Single diffusion
Double diffusion

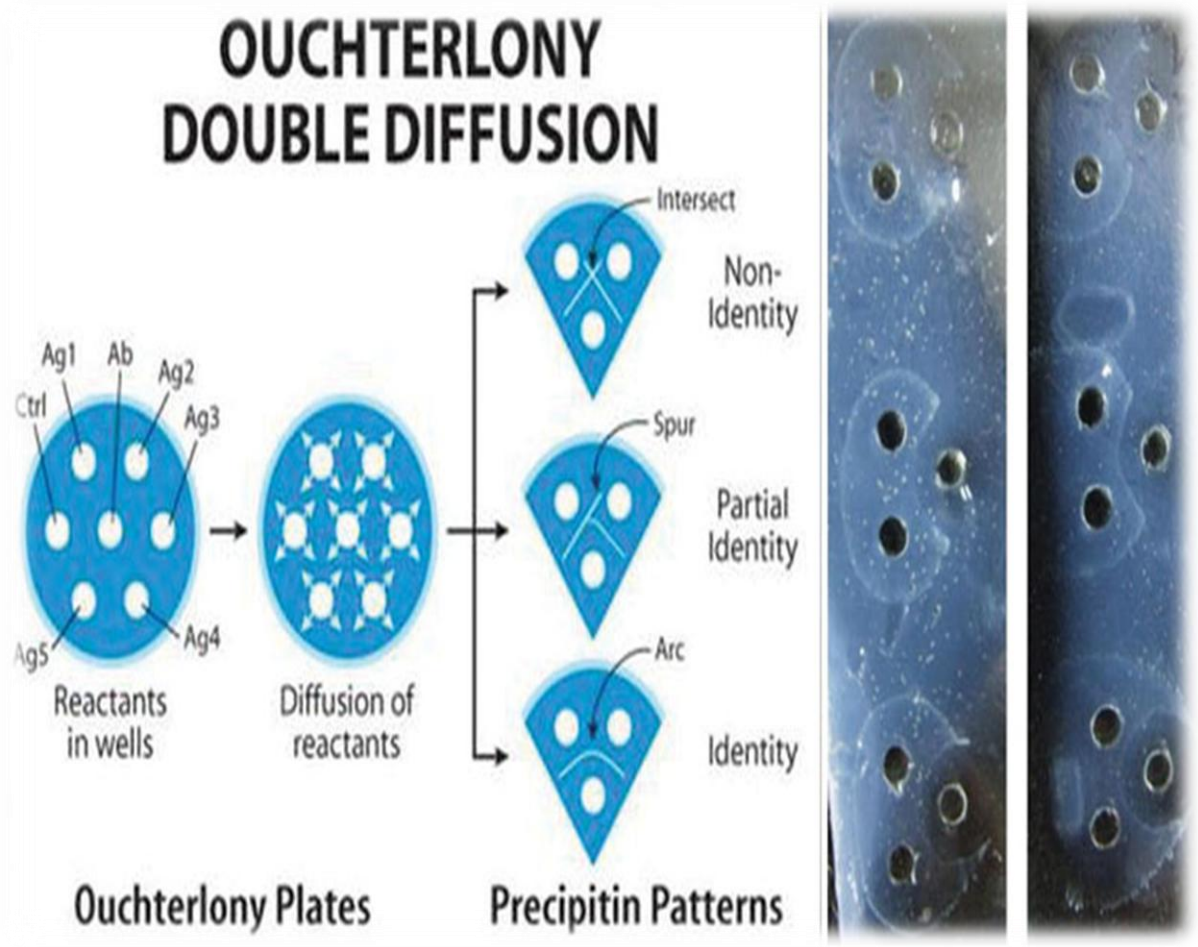
D- Double Diffusion in Two Dimensions

- It is also known as **agar gel diffusion** in which wells are punched in agar gel
- The antiserum is placed in the central well and **different Ags are placed in the surrounding wells**
- The slide is then placed in a moist chamber to prevent drying and to allow diffusion for ٢٤ hours or more
- The result is **formation of precipitation bands** where they meet in optimum proportion
- If two adjacent Ags are identical, the lines of precipitate formed will fuse.
- If they are not identical, the lines will cross each other.

Immunoelectrophoresis

- It is a combination of electrophoresis and agar gel diffusion
- • The test is done in two steps
- - In first step, the Ag is subjected to electrophoretic separation in agar gel
- - In second step, a trough is cut parallel to and slightly away from the path of electrophoretic separation and is filled with antiserum and allowed to diffuse
- • The Ag and Ab diffuse towards each other and form precipitation bands


1
Semiosolid agar slide
Trough
Well for antigen
2
Antigen well filled with human serum (Antigen)
3
Separated antigen by electrophoresis
5
Antiserum through filled with antiserum to whole human serum
4
Serum and antiserum allowed to diffuse into agar
6
Precipitin lines are formed for individual serum proteins



Radioimmunoassay

A radioimmunoassay (RIA) is an immunoassay that uses radiolabeled molecules in a stepwise formation of immune complexes. A RIA is a very sensitive in vitro assay technique used to measure concentrations of substances, usually measuring antigen concentrations (for example, hormone levels in blood) by use of antibodies.

Although the RIA technique is extremely sensitive and extremely specific, requiring specialized equipment, it remains among the least expensive methods to perform such measurements. It requires special precautions and licensing, since radioactive substances are used.[citation needed]

In contrast, an immunoradiometric assay (IRMA) is an immunoassay that uses radiolabeled molecules but in an immediate rather than stepwise way.

A radioallergosorbent test (RAST) is an example of radioimmunoassay. It is used to detect the causative allergen for an allergy.

Method

Classically, to perform a radioimmunoassay, a known quantity of an antigen is made radioactive, frequently by labeling it with gamma-radioactive isotopes of iodine, such as ١٢٥-I, or tritium[١] attached to tyrosine. This radiolabeled antigen is then mixed with a known amount of antibody for that antigen, and as a result, the two specifically bind to one another. Then, a sample of serum from a patient containing an unknown quantity of that same antigen is added. This causes the unlabeled (or "cold") antigen from the serum to compete with the radiolabeled antigen ("hot") for antibody binding sites. As the concentration of "cold" antigen is increased, more of it binds to the antibody, displacing the radiolabeled variant, and reducing the ratio of antibody-bound radiolabeled antigen to free radiolabeled antigen. The bound antigens are then separated and the radioactivity of the free(unbound) antigen remaining in the supernatant is measured using a gamma counter. This value is then compared to a standardised calibration curve to work out the concentration of the unlabelled antigen in the patient serum sample.RIAs can detect a few picograms of analyte in an experimental tubes if using antibodies of high affinity.

This method can be used for any biological molecule in principle and is not restricted to serum antigens, nor is it required to use the indirect method of measuring the free antigen instead of directly measuring the captured antigen. For example, if it is undesirable or not possible to radiolabel the antigen or target molecule of interest, a RIA can be done if two different antibodies that recognize the target are available and the target is large enough (e.g., a protein) to present multiple epitopes to the antibodies. One antibody would be radiolabeled as above while the other would remain unmodified. The RIA would begin with the "cold" unlabeled antibody being allowed to interact and bind to the target molecule in solution. Preferably, this unlabeled antibody is immobilized in some way, such as coupled to an agarose bead, coated to a surface, etc. Next, the "hot" radiolabeled antibody is allowed to interact with the first antibody-target molecule complex. After extensive washing, the direct amount of radioactive antibody bound is measured and the amount of target molecule quantified by comparing it to a reference amount assayed at the same time. This method is similar in principle to the non-radioactive sandwich ELISA method.

ELISA

Enzyme Linked Immunosorbent Assay

Definitions: Antibodies (also known as immunoglobulins abbreviated Ig) are gamma globulin proteins that are found in blood and are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses.

- **Antigens**

A substance that when introduced into the body
stimulates the production of an antibody

- **Immunoassay**

A laboratory technique that makes use of the binding between an antigen and its homologous antibody in order to identify and quantify the specific antigen or antibody in a sample

- **Analyte**

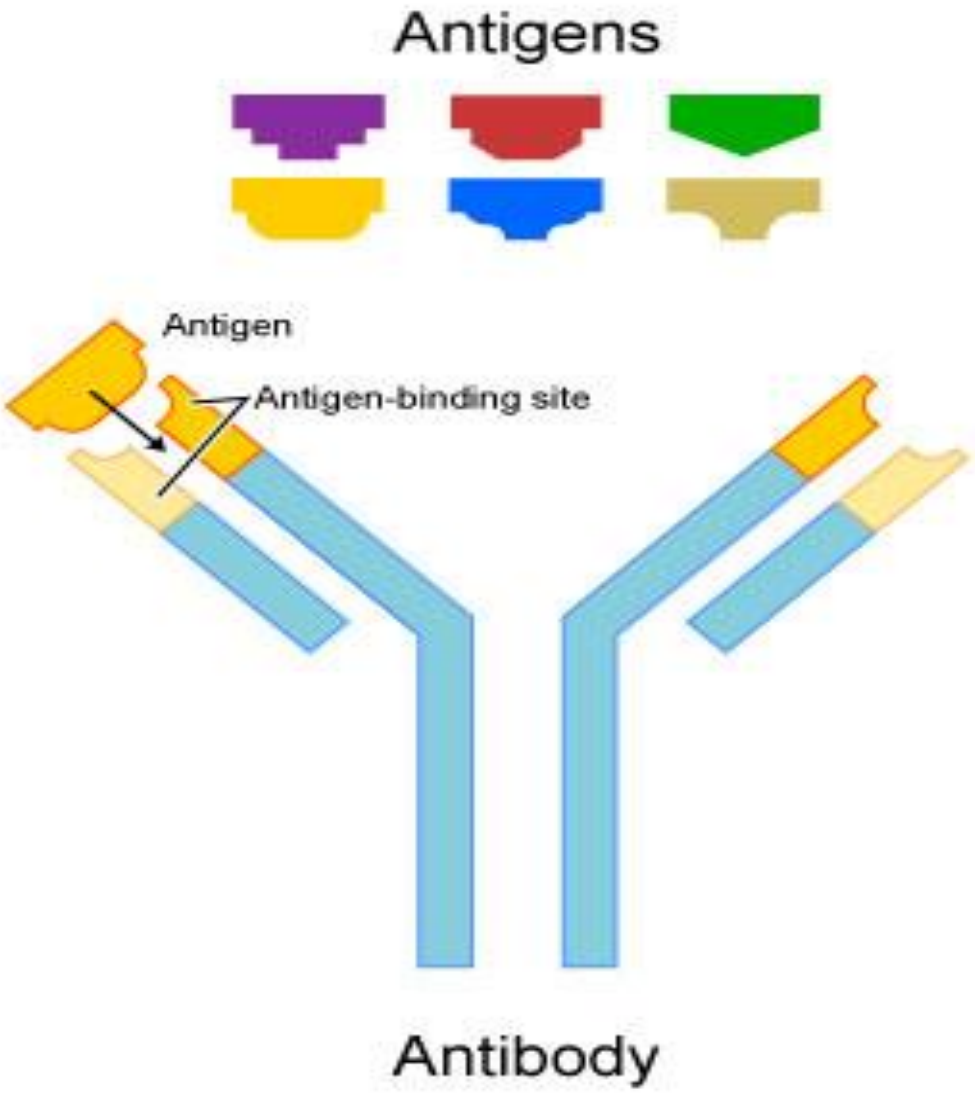
The sample being analyzed and in immunoasssays the analyte is either Antibody or Antigen

Antigen

- Is present naturally in the body like hormones
- Is manufactured in special disease status for example human chorionic gonadotrophin hormone (HCG) which is normally produced by cells of the placenta in pregnancy is found in the body in some types of cancer

Introduction

- **The Antibody:** An immunoglobulin, a specialized immune protein, produced because of the introduction of an antigen into the body, and which possesses the remarkable ability to combine with the very antigen that triggered its production (specific affinity)
- The antibody recognises and bind to the antigenic determinant region of the antigen


Antigens
Antigen
Antigen-binding site
Antibody

ELISA technique

Is a biochemical technique used mainly in immunology to detect the presence of an antibody or an antigen in a sample.

- The technique is divided into

  ١- Competitive ELISA

  ٢- Sandwich ELISA (also called direct ELISA)

  ٣- Indirect ELISA

  Sandwich ELISA

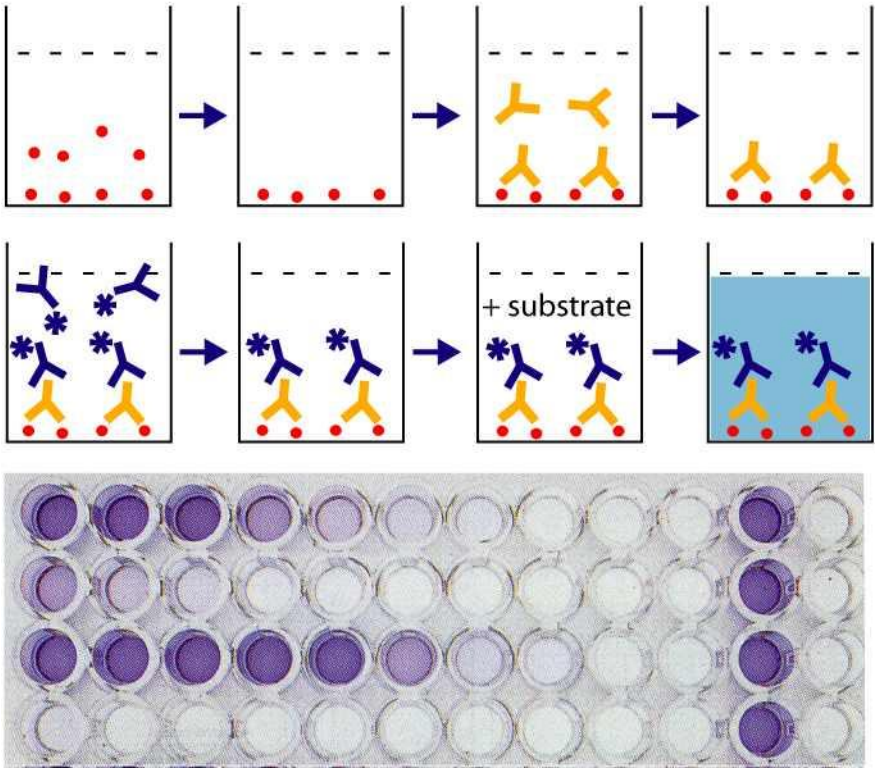
- Prepare a surface to which a known quantity of capture antibody is bound.
- Block any non specific binding sites on the surface
- Apply the antigen-containing sample to the plate.

Sandwich ELISA-Cont

- Wash the plate, so that unbound antigen is removed.
- Apply enzyme linked primary antibodies as detection antibodies which also bind specifically to the antigen.
- Wash the plate, so that the unbound antibody-enzyme conjugates are removed.
- Apply a chemical which is converted by the enzyme into a coloured product.

- Measure the absorbency of the plate wells to determine the presence and quantity of antigen

Indirect ELISA



An example of an ELISA experiment

Before starting the work read kit instruction carefully

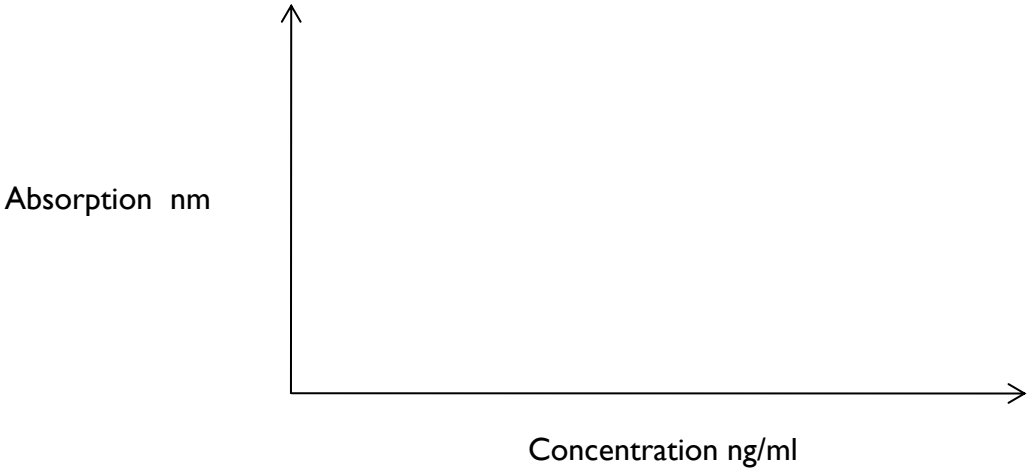
١- The ٩٦ well plate is labeled carefully and the first wells are used to draw the standard curve

An example of an ELISA experiment-Cont

- The sample is added to plate in duplicate or triplicate and then the mean result is calculated
- The quality control sample which is provided with the kit is treated as the test samples

Results

- After reading the results the standard curve is drawn were the concentration is blotted on the X-axis and the absorbance on the Y-axis



Results-cont

- The standards concentrations is specified on the x-axis and the reading of each standard is specified on the y-axis and the standard curve is drawn

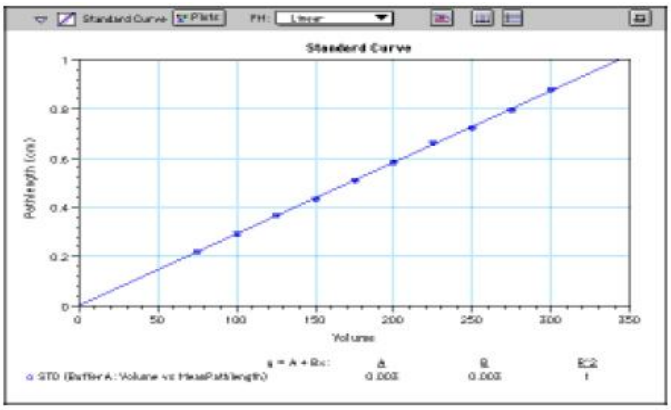


Figure 8: The calibration curve relating well volume to pathlength

- This standard curve is used to determine the unknown concentration of each sample by finding the opposite concentration to the absorbance

▶ The quality control sample concentration is determined from the standard curve and if the result is in the range given by the kit manufacturer the results could be accepted

▶ الاختبار البعدي (Post-Test)

Q١/ What are Double Diffusion in Two Dimensions

Q٢/What are The technique is divided

Q٣/ Put True or false of the following

١- The standards concentrations is specified on the x-axis and the reading of each standard is specified on the y-axis and the standard curve is drawn

٢- A radioimmunoassay (RIA) is an immunoassay that uses radiolabeled molecules in a stepwise formation of immune complexes. A RIA is a very sensitive in vitro assay technique used to measure concentrations of substances

٣- **ELISA** :Antibodies (also known as immunoglobulins abbreviated Ig) are gamma globulin proteins that are found in blood and are used by the immune system to identify and neutralize foreign objects

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الاسبوع الرابع والخامس والسادس والسابع

المحتوى:

-The immune response to infection

-Immune responses to extracellular bacteria

- Septicaemia and shock

- Immunity to encapsulated bacteria

- Immunity to viruses

▶ الاختبار القبلي (Pre-Test)

Q١/What are Mechanical Barriers
Q٢/ What are The immune response to infection?

The immune response to infection

١. *Non-specific immunity*

The immune system has evolved to deal with infectious pathogens. There are several lines of host defence.

When evaluating the cause of infection in any patient it is important to exclude non-specific immune defects.

The following checklist serves as a guide.

(١)Mechanical barriers

(٢) Disturbance of drainage.

(٣) Secretions

(٤) Disturbed microbial flora

(٥) Specific Immunodeficiency

١. *Mechanical Barriers*

Mechanical barriers are a crucial first line of defence. It would be impossible to provide an exhaustive

list. Two examples are:

(١) susceptibility of burns patients to infection

(٢) recurrent meningitis in patients with occult skull fracture

٢. *Disturbance of drainage and necrotic or poorly vascularised tissue.*

Phagocytes, immune cells and the soluble components of the immune system cannot gain access to

pockets of fluid or poorly vascularised tissue.

Therefore adequate drainage of secretions plays a crucial role in infection prevention and treatment.

Common examples which predispose to infection include urinary tract obstruction but in general

accumulation of fluid at any site is associated with increased risk. This is why surgical operation

sites are so carefully drained. A less obvious example is the susceptibility of patients with cystic

fibrosis to respiratory infections because of the failure to drain secretions. Aggressive treatment of

these patients with physiotherapy, mucolytic agents and antibiotics has dramatically reduced the

severe lung damage associated with this disease.

Tears, saliva, bile, pancreatic, mucus and even sebaceous secretions help protect the surfaces they

flow over, and obstruction is associated with infection.

For the same reasons, necrotic poorly vascularised tissue is readily infected because components of

the immune system cannot get access. This is why surgical debridement of wounds is so important

and why patients with poor circulation (atherosclerosis and diabetes mellitus) have an increased risk

of infection.

٣. *Secretions*

Secretions contain a number of enzymes and factors which help inhibit bacterial growth. Acid

secretions of the stomach help to sterilise the partially-digested food that enters the small intestine.

In the past treatment of duodenal ulcer involved severing the vagus nerve to reduce acid secretion in

the stomach. The lack of bacteriocidal acid in the stomach predisposes these patients to enteric

infections. Other examples include the low pH in the vagina which prevents bacterial colonisation,

and also such enzymes as lysozyme in tears.

٤. *Normal bacterial flora*

There are large numbers of bacteria on the skin, in the mouth and in the large intestine. Normally these are

non-invasive commensal microorganisms that do not cause disease. The presence of this normal bacterial

flora helps to inhibit the invasion of pathogenic bacteria. Loss of the normal flora associated with the use of

antibiotics or excessive use of antiseptic solutions can provide an opportunity for pathogenic bacteria to

colonise the vacated tissues. Staphylococcal enteritis is commonly associated with the use of antibiotics.

٢. *Specific Immune Responses*

The immune system has evolved to deal with infectious pathogens. Although all pathogens are different

from each other, they can be subgrouped by the pattern of the immune response that they evoke. In general

pathogens may be subdivided as follows:

١. *Types of pathogen*

(١) Extracellular bacteria and toxins

(٢) Viruses

(٣) Intracellular bacteria

(٤) Intra and extracellular protozoa

(٥) Extracellular parasites

(٦) Encapsulated bacteria

Like most battles, immune responses have a cost. In some instances the immune response kills the

patient rather than the pathogen which is relatively harmless. It is crucial to appreciate, therefore that

it is important to switch off as well as switch on normal immune responses, and that evolutionary

pressure has promoted defence strategies which are effective but relatively safe for the host.

٢. *Immune responses to extracellular bacteria*

Immunity to extracellular and intracellular bacteria is dependent on different effector immune cells.

The following example illustrates in a simplified outline the sequence of events leading to an immune

response against bacteria.

Initial phase and the activation of the innate immune system

Rapidly dividing streptococci in a surgical wound locally activate complement in the extracellular

tissue. Proinflammatory complement fragments like C٣a and C٥a recruit neutrophils and activate local

mast cells which increase blood flow and release a further cascade of proinflammatory mediators.

Uptake of antigens for presentation

Recruited neutrophils phagocytose complement coated bacteria and kill them. Apoptotic neutrophils

are taken up by local Langerhans cells which process extracellular protein antigens derived from the

bacteria and present them mainly in association with HLA class II.

Langerhans cells differentiate into dendritic cells under the influence of inflammatory cytokines like

tumour necrosis factor and migrate to the T zones of lymph nodes via the lymphatics where they

present antigen to T cells.

T cell priming

T cells migrating form the blood through high endothelial venules (HEV) in lymph nodes "look" for

antigen expressed by dendritic cells. Antigen-specific T cells become primed by a combination of

antigen, costimulatory molecules and cytokines (interleukin-١٢, (IL١٢)) expressed by activated

dendritic cells. Primed T cells are then able to help other effector cells.

Th1 T cells promote inflammation at the site of infection

Two principal types of effector T cells have been described:Th١ cells are inflammatory T cells which

secrete interferon-g (IFNg) interleukin-٢ (IL٢) and other cytokines which recruit inflammatory cells to

inflamed tissue. Their development is promoted by the cytokine IL-١٢. Their pathway of migration is

distinct from Th٢ cells in that they migrate via the blood and recognise

receptors on inflamed endothelium, hence gaining access to infected tissue.

There they activate macrophages via IFNg and by release of proinflammatory

cytokines ensure the blood supply is maintained. *The acute phase response*

Release of interleukin-١ and ٦ by macrophages into the bloodstream stimulates the liver to make an acute phase response which includes increased synthesis of many serum proteins including complement components which are being consumed at the inflamed site, thus ensuring a supply line

of immune components. One protein, C-reactive protein (CRP) functions like a primitive antibody by binding to and opsonising bacteria. Because CRP is potently upregulated, it is a useful indicator of inflammation, especially bacterial infection. *Th2 cells promote B cell activation and differentiation* Th٢ T cells promote antibody formation and secrete interleukins-٤, ٥ and ١٠ . Recirculating B cells

when triggered through their antigen-specific receptors to take up and process soluble bacterial antigens, migrate to the T cell areas seeking "help". It is probable that activated B cells express molecules which induce antigen-specific CD٤ T cells to differentiate into Th٢ cells. These T cells

help B cells to undergo clonal expansion and affinity maturation within structures called germinal centres. As a consequence of this, high titre, high affinity antibody is generated which is effective at neutralising bacterial toxins. Class switching to IgG antibodies promote the much more efficient opsonisation and removal of bacteria by phagocytes.

The type of antibody evoked by bacterial antigens is dependent on location. At mucosal sites, predominantly IgA is produced, which is better at neutralisation than inflammation. However, IgA unlike IgG antibodies do not protect against sepsis. In the lung, IgG is the most important antibody,as control of respiratory infections is dependent on the efficient removal of bacteria by neutrophils

and IgG. *B and T cell memory*

In addition to generating effector B and T cells, memory B and T lymphocytes are produced which

make rapid and more efficient responses upon reexposure to the infection.

٣. *Septicaemia and shock*

Neutrophils cannot remove bacteria which are in the blood. The spleen plays a crucial role in the

removal of pathogens which are not coated with antibody from the bloodstream. As a consequence,

splenectomy is an important risk factor for overwhelming sepsis with bacteria, and malaria.

Antibody coated bacteria are also efficiently removed by Kupffer cells (macrophages) in the liver.

The susceptibility to infection in liver failure is partly due to the lack of synthesis of immune

components and partly due to the defective phagocytosis.

Endotoxic shock is a clinical condition with multiorgan system failure due to circulatory and

respiratory collapse. It is mainly due to the exaggerated release of inflammatory mediators by

macrophages and immune cells, particularly tumour necrosis factor.. Mice deficient in tumour

necrosis factor are protected from shock induced by lipopolysaccharide but on the other hand are

more likely to die from overwhelming bacterial sepsis. This illustrates the fine line that the immune

system has to tread between evoking protective immunity and killing the host. It emphasises the

need to have potent mechanisms for switching off immune responses as well as on.

٤. *Immunity to encapsulated bacteria*

To evade the immune response, certain strains of bacteria have become encapsulated with a

polysaccharide coat.. Encapsulated bacteria grow less well than their nonencapsulated counterparts

but can evade the immune system as they activate complement poorly, and immunity is dependent

on generating antibody to the polysaccharide capsule. Three types of bacteria are clinically

important in humans:

Neisseriae meningitidis

Pneumococci

Haemophilus Influenzae

All these strains of bacteria can cause overwhelming sepsis and meningitis, and the latter two are

common causes of pneumonia and secondary bacterial lung infections. The polysaccharide capsule

of these bacteria is poorly degraded by human cells and cannot elicit conventional T cell help.

Although the mechanism of antibody formation is poorly understood, polysaccharides probably

activate B cells directly, causing them to migrate to the T cell areas of secondary lymphoid tissue.

Here they probably receive accessory signals from macrophage like cells, but they probably do not

require T cell help. In normal individuals antibody is sufficient to opsonise and remove these

bacteria.

For reasons that are not understood, children less than ٢ years of age in particular, make poor

responses to polysaccharide antigens derived from the above bacteria. In the first few months of life,

infants are protected by maternal immunoglobulin, but as this wanes the incidence of infection rises.

This problem has been addressed by conjugating sugar epitopes derived from the polysaccharides

with conventional protein antigens. These conjugate vaccines induce efficient antibody responses

in infants and have substantially reduced the mortality and morbidity from *H. Influenzae.*

٥. *Immunity to viruses*

Neutralising antibody plays a crucial role in eliminating intact viruses by preventing the infection of

other cells. Essentially the same mechanism which elicits antibody responses to other protein

antigens (described above) operates for viruses.

To combat the intracellular phase of viral replication, the immune system has developed a number of

strategies. Most cells are capable of secreting interferon a and b which inhibit viral replication.

Double stranded RNA (i.e. viral RNA) is particularly efficient at inducing interferons, which have

been used therapeutically to help eliminate persistent viral infections in humans.

The second important mechanisms is the generation of CD٨ cytotoxic T cells. To combat viral

infection, all nucleated cells have machinery for generating peptide fragments from cytosolic (self

and viral) proteins (the proteasome). Peptide fragments derived from cytosolic proteins are

transported (by tap proteins) into the endoplasmic reticulum where they are loaded onto nascent

class I molecules and transported to the cell surface where they can be seen by CD٨ cytotoxic T

cells.

CD٨ cells are normally not primed directly by virally infected cells. One possibility is that apoptotic

virally infected cells are phagocytosed by Langerhans cells. Antigen-processing by Langerhans

cells appears to be different when the antigen is taken up by this pathway, and leads to antigen

presentation on HLA class I and II molecules. CD٤ and CD٨ T cells recognise antigen on the

dendritic cell leading to T cell help from CD٤ cells (IL٢) for the development and expansion of

cytotoxic CD٨ T cells.

Once primed, cytotoxic CD٨ T cells migrate out into tissue and can kill virally infected targets. CD٨ T

cells play a crucial role in regulating viral infections. In humans immunosuppression of T cells is

associated with uncontrolled viral replication, particularly of Herpes viruses like Cytomegalovirus

(CMV) and Epstein Barr Virus. Kaposi's Sarcoma seen in HIV infection is another Herpes virus

associated tumour.

٦. *Natural killer cells*

To evade killing by cytotoxic T cells, complex viruses like CMV downregulate the expression of class

I molecules, by preventing their expression on the surface of the virally infected cell. To combat this

strategy, natural killer cells (NK) have evolved. These cells express receptors with restricted

polymorphism which recognise self class I HLA antigens. These receptors are inhibitory, and NK

cells are not activated by self cells which express normal levels of class I. In contrast, CMV infected

cells which have downregulated MHC class I expression, are killed.

Immunity to viruses is therefore quite complex and depends on both cytotoxic CD٨ T cells and NK

cells, and neutralising antibody.

٧. *Immunity to non-viral intracellular pathogens*

Normally neutrophil killing is adequate for most bacteria. However, several organisms have

developed strategies which evade intracellular killing. These include:

Bacteria like *Mycobacterium Tuberculosis*, *Salmonella* and *Listeria Monocytogenes*,

Protozoa like *Toxoplasma gondii* and *Cryptosporidiosis*.

These organisms are resistant to killing by neutrophils. Immunity to these organisms is dependent

on activating aggressive killing mechanisms in macrophages, which are distinct from normal

bacteriocidal killing in neutrophils. IFNg secreted by Th١ CD٤ and CD٨ T cells is the crucial cytokine

which evokes this response in that deficient mice and men suffer from intractable intracellular

infections with the above organisms. This can be treated with exogenous IFNg.

٨. *Immunity to parasites*

The final subclass of infection is parasites which are generally complex organisms which invade

through mucosal surfaces or the skin. Parasites have sophisticated mechanisms for evading the

immune response and the most effective strategy is to prevent infection in the first place.

Anaphylactic IgE mediated responses against parasites evolved to prevent parasites gaining access

to the host by expelling the parasite as a consequence of the degranulation of mast cells and release

of vasoactive substances, particularly histamine.

The generation of IgE is dependent on the Th٢ cytokine IL٤. IL٥ also secreted by Th٢ cells recruits

eosinophils which can kill parasites by exocytosing a cytotoxic protein, cationic basic protein.

Th٢ responses are maintained at mucosal sites by the following mechanism. IL٤ reinforces Th٢

responses by inhibiting Th١ cell development. Activation of mast cells which are primarily located at

mucosal sites and under the skin leads not only to the release of histamine and other inflammatory

mediators which lead to expulsion of parasites, but also IL٤ secretion which reinforces the local Th٢

responses.

٩. *Summary*

Because different effector cells play different roles in immunity to different types of infection, the

clinical presentation often gives a clue to the underlying immunodeficiency.

▶ الاختبار البعدي (Post-Test)

Q١/ What are viral immunity?

Q٣/Whate are Immune responses to extracellular bacteria

Q٤/Whate are Immunity to encapsulated bacteria

الاسبوع الثامن والتاسع

▶ الاختبار القبلي (Pre-Test)

Q١/ Compare with Innate immunity and Adaptive immunity

Q٢/ What are immune cells include

Cells Of Immune System

Cells involved in specific and nonspecific immune mechanisms are:

Innate immunity	Adaptive immunity
■ Granulocytes (i.e. neutrophils) ■ Macrophages ■ Dendritic cells ■ Natural killer (NK) cells	■ Lymphocyte ■ B cells ■ T cells ■ Cytotoxic T cells (CTLs) ■ Helper T cells (Th) ■ Memory cells

Hematopoitic leucocytes

The origin is the bone marrow : the immune cells include :

١- Lymphoid :with production of lymphocytes

- Many types; important in both humoral and cell-mediated immunity
- B-cells produce antibodies
- T- cells

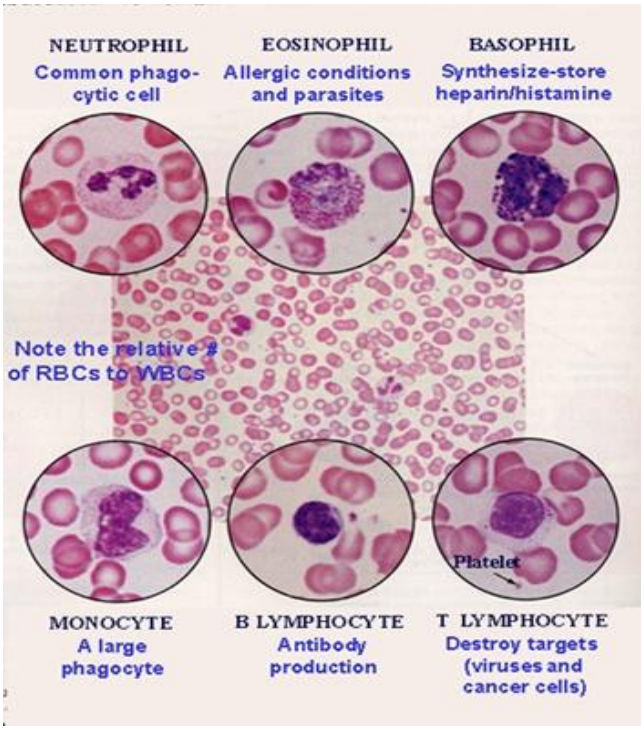
- Cytotoxic T cells
- Helper T cells

- Memory cell

- NK cells

* T-lymphocytes: characteristics :

- Antigen specific cells carrying CD٣ complex, CD٤, CD٨
- Dominant blood lymphocytes (٧٠٪)
- Produce cytokines
- Activation of other cells (Th CD٤)
- Suppressors for others (Ts CD٨)



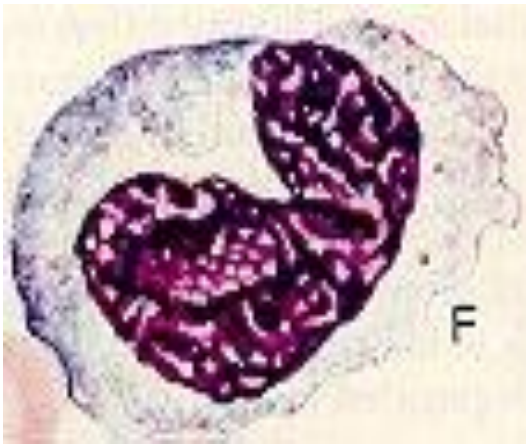
lymphocyte

* B-lymphocytes:

- Antigen specific cells with surface receptor
- Less common lymphocytes (٢٠٪)
- Responsible for antibody production

* NK, K cells:((Natural killer cell)

- NK cells do not require prior immunization or activation
- They attach to ‘target’ cells
- Cytotoxic granules are released onto surface of cell
- Effector proteins penetrate cell membrane and induce programmed cell death
- Not antigen specific
- Carry Fc receptors , NK-target cell receptor



٢- Monocytic myeloid

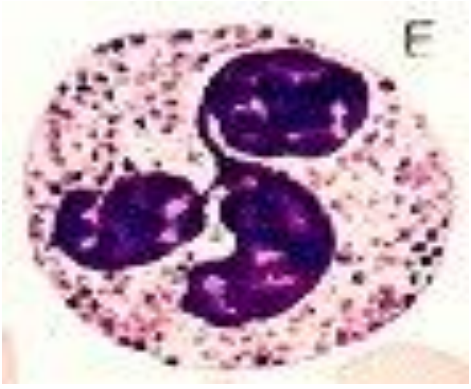
a- *Monocyte*-tissue macrophages:

- Monocyte is a young macrophage
- There are tissue-specific macrophages

- MØ process antigen, are phagocytes and produce cytokines (esp., IL١ & IL٦)
- Non specific
- Carry Fc receptors
- Phagocytic
- Antigen processing and presenting cells

b- Neutrophils:

- Granulocyte



- Phagocytes
- Short life span (hours)
- Very important at “clearing” bacterial infections
- Cytoplasmic granules
- Non specific
- Carrying Fc, complement molecules

Neutrophil

c- Eosinophils:

- A granulocyte
- A cell-killing cells

- Orange granules contain toxic compounds
- Produce allergic mediators and Important in parasitic infections
- Non specific
- Carrying Fc receptor

Basophil

.

d- Basophils and Mast cells:

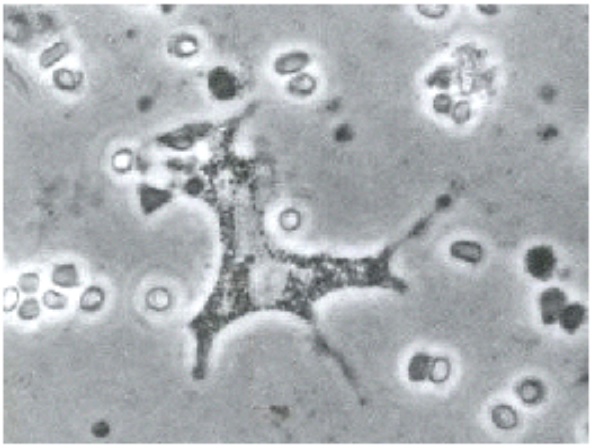
- A granulocyte
- A cell-killing cells
- Blue granules contain toxic and inflammatory compounds
- Produce allergic mediators so Important in allergic reactions
- Non specifc
- Carrying Fc receptors

.

e-Dentritic cells :

- Found mainly in lymphoid tissue
- specialized APCs (professional APCs)Function as antigen presenting cells (APC)
- Most potent stimulator of T-cell response

APC : Antigen presenting (or processing) cells



Cytokines

- Low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune system

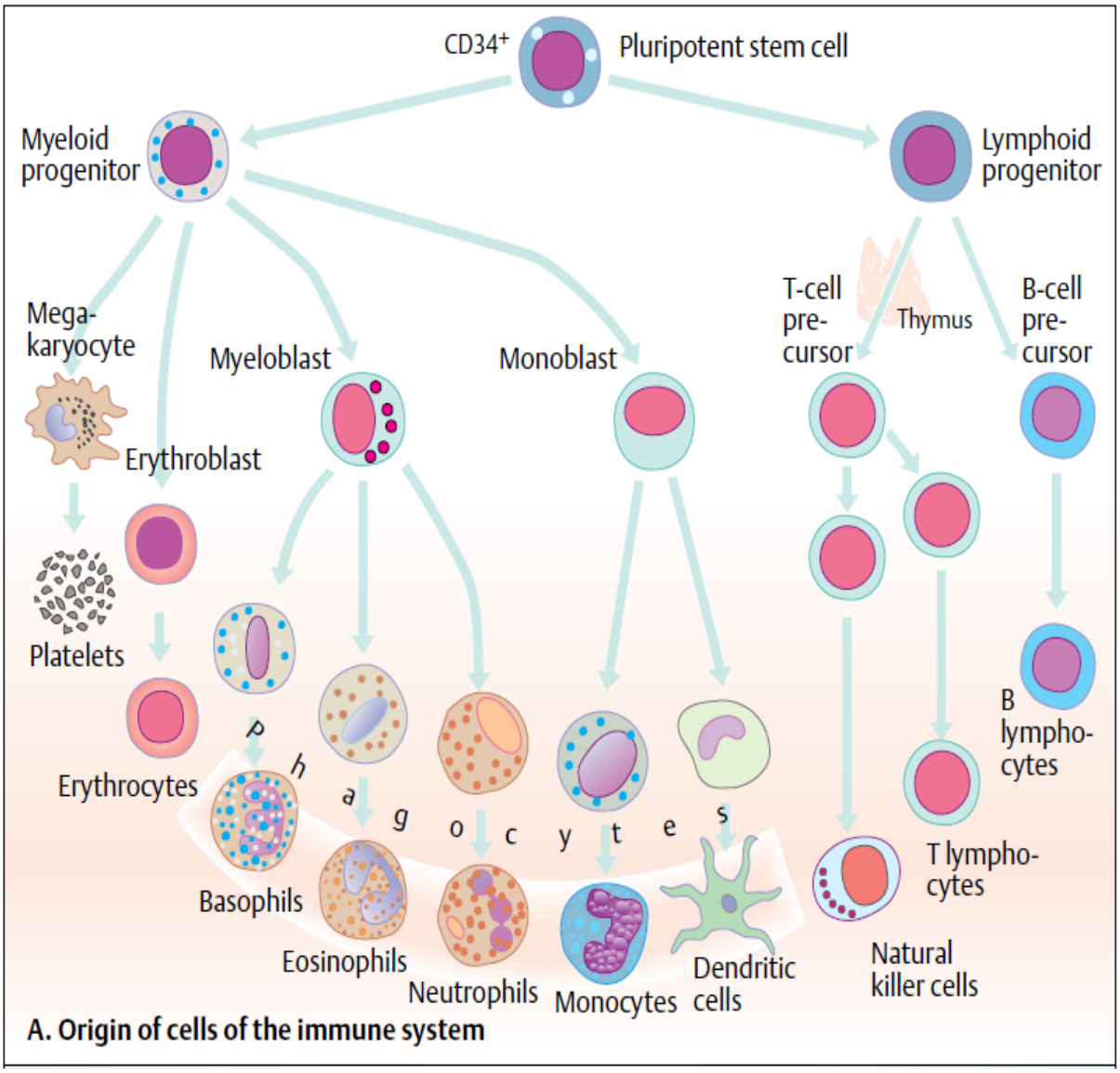
-Innate immune system

- Macrophages and Dendritic cells : produce
  - Tumor necrosis factor-alpha (TNF-α)
  - Interleukin-١ (IL-١)
  - Interleukin-١٢ (IL-١٢)

-Adaptive immune system

- T-lymphocytes: produce
  - Interleukin-٢ (IL-٢)
  - Interleukin-٤ (IL-٤)

The origin of Immune cells



▶ الاختبار البعدي (Post-Test)

Q١/defined Cytokines

Q٢/ What are produce Macrophages and Dendritic cells

Q٣/ What are produce T-lymphocytes:

الاسبوع العاشر والحادي عشر

▶ الاختبار القبلي (Pre-Test)

Q١/What are joint and muscle diseases
Q٢/What are Pattern of joint disease

joint and muscle diseases

Patterns of joint disease

Joint diseases fall into two broad categories:

١. Degenerative conditions of cartilage (osteoarthritis)
٢. Disorders characterized by inflammation of the joint lining or synovium (inflammatory arthritis or synovitis).

The healthy synovial lining (Fig.١) consists of a single layer of cells overlying loose, well-vascularized stromal tissue.

The lining cells are of two kinds: one fibroblastic, which synthesizes the proteoglycans, which act as a lubricant within the joint, and one derived from macrophages, which probably have a scavenging function. Unlike most body surfaces, free passage of intercellular fluid can occur across the synovial membrane, a factor that may explain why antigens tend to be deposited within the joint.

The synovial response to injury is relatively limited, and the *pathology of most forms of inflammatory arthritis consists of hyperplasia of the lining layer and cellular infiltration of the vascular tissues beneath the lining*. Cytokine production in chronic synovial inflammation may also be limited in its variety. Most synovial diseases show some response to treatments that block the action of tumor necrosis factor (TNF)-α.

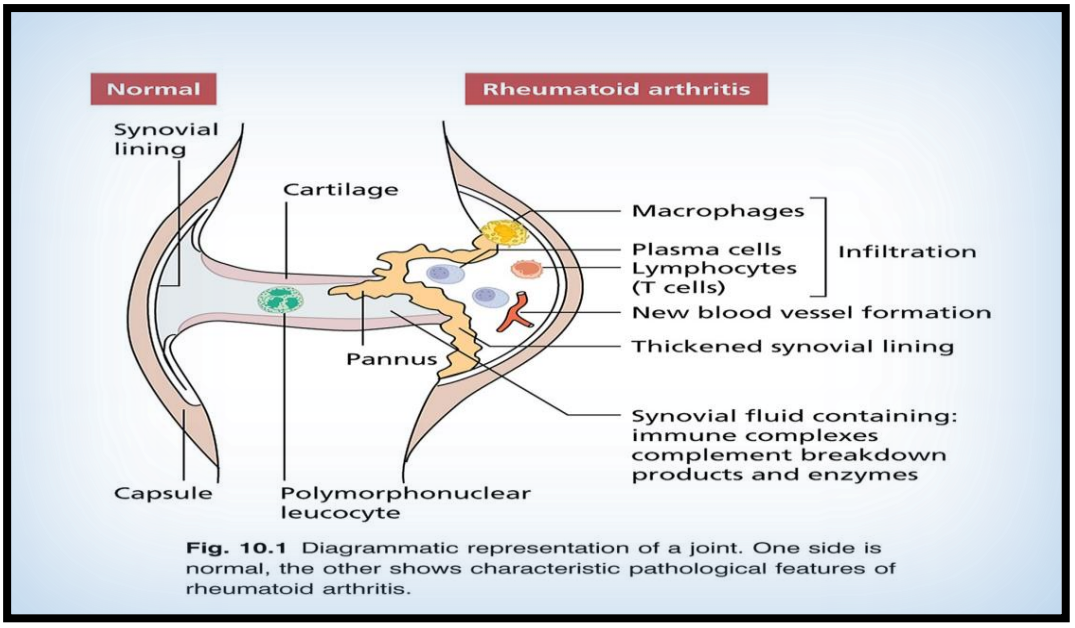


Fig.١: joint in normal & in arthritis

Pattern of joint disease

- Mono-articular
- Oligo-articular
- Poly-articular

Rheumatoid arthritis [RA]

Rheumatoid arthritis is a common, persistent, autoimmune disease, chronic inflammatory disorder that can affect joints in symmetrical fashion and result in cartilage destruction and bone deformity. RA is a common disease affecting ١–٢٪ of the adult population and is twice as common in women as men. It is most common between the ages of ٢٥ and ٥٥ years.

Etiology

١. Arthritogenic agents:
   a. viruses such as retroviruses, EBV, HSV and rubella au
   b. bacteria such as mycoplasma, mycobacteria, enteric bacteria
٢. autoantibodies formation such as rheumatoid factor

Classification criteria

١. morning stiffness
٢. arthritis > ٣ joints area simultaneously
٣. hand joints arthritis
٤. symmetrical arthritis
٥. serum rheumatoid factor
٦. radiographic changes

Symptoms and Signs

١. Fatigue
٢. Joint pain
٣. Joint tenderness
٤. Joint swelling
٥. Joint redness
٦. Joint stiffness (morning stiffness last for hours of increased pain)
٧. Loss of joint range of motion (disability)
٨. Joint deformity
٩. Many joints affected (polyarthritis)
١٠. Both sides of the body affected (symmetric)

Diagnosis

Diagnosis of RA depends on:

١. physical examination
٢. laboratory results which includes:
a. CBC & ESR
b. RF screening test
c. Anti-CCP estimation
d. CRP and complement detection
e. ANA (antinuclear antibodies) detection
f. Synovial fluid analysis

.

Diagnostic finding

١. High titre serum rheumatoid factor
٢. Female sex
٣. High levels of acute phase proteins (ESR, CRP)
٤. High levels of disability
٥. Extra-articular disease
٦. Radiological evidence of joint damage
٧. High titer anti-citrullated peptide (anti-CCP) antibodies & antinuclear Abs
٨. Anemia and thrombocytopenia
٩. Synovial fluid analysis show leukocytosis > ٢٠٠٠/µl

Synovial fluid analysis

١) Inflammatory synovial fluid show WBCs > ٢٠٠٠/ µl cell generally from ٥٠٠٠-٥٠٠٠٠/ µl
٢) Neutrophil predominance (٦٠-٨٠٪) in synovial fluid in contrast with monocytes predominance synovium

٣) Since there are transport defect, the glucose level of pleural, pericardial and synovial fluid in patients with rheumatoid arthritis are often low compared to serum glucose level

Imaging studies

١. Radiography
   a. Joints show bony erosion, cysts, osteopenia, joint space swelling, calcification, narrowed joints space, deformities, separations & fractures
   b. Cervical spine
٢. Imaging studies
a. CT and MRI of joints & cervical spines b. Ultrasound

Treatment

- No cure for RA, treatment for symptoms improvement & slow disease progression
- Medication can be achieved with using of two main classes: analgesics such as NSAIDs and disease- modifying anti-rheumatic drugs (DMARDs)

- Hypersensitivity refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.
- -Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
- Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

TYPE I HYPERSENSITIVITY

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause a range of symptoms from minor inconvenience to death. The reaction usually takes ١٥ - ٣٠ minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (١٠ - ١٢ hours).

Immediate hypersensitivity is mediated by IgE. The primary cellular component in this hypersensitivity is the mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.

The mechanism of reaction involves

١- preferential production of IgE, in response to certain antigens (often called allergens).

٢- The precise mechanism as to why some individuals are more sensitive to type-I hypersensitivity is not clear. However, it has been shown that such individuals preferentially produce more of TH٢ cells that secrete IL-٤, IL-٥ and IL-١٣ which in turn favor IgE class switch.

٣- IgE has very high affinity for its receptor (Fcε; CD٢٣) on mast cells and basophils.

A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances (figure ١). Cross-linking of IgE Fc-receptor is important in mast cell triggering.

The agents released from mast cells and their effects are listed in Table ١. Mast cells may be triggered by other stimuli such as exercise, emotional stress, chemicals (e.g., photographic developing medium, calcium ionophores, codeine, *etc.*), anaphylotoxins (*e.g.*, C٤a, C٣a, C٥a, *etc.*). These reactions, mediated by agents without IgE-allergen interaction, are not hypersensitivity reactions, although they produce the same symptoms.

Table ١. Pharmacologic Mediators of Immediate Hypersensitivity	
MEDIATOR	
Preformed mediators in granules	
histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
tryptase	proteolysis
kininogenase	kinins and vasodilatation, vascular permeability, edema
Newly formed mediators	

leukotriene B_4	basophil attractant
leukotriene C_4, D_4	same as histamine but ١٠٠٠x more potent
prostaglandins D_2	edema and pain
PAF	platelet aggregation and heparin release: microthrombi

▶ الاختبار البعدي (Post-Test)

Q١/What are Rheumatoid arthritis [RA] Diseases
Q٢/ how are Diagnosis Rheumatoid arthritis
Q٣/What are Symptoms and Signs Rheumatoid arthritis

الاسبوع الثاني عشر والثالث عشر

▶ الاختبار القبلي (Pre-Test)

Q١/What are Type II Hypersensitivity disease

Q٢/ What are Comparison of Different Types of hypersensitivity

TYPE II HYPERSENSITIVITY

Type II hypersensitivity is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. Drug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time is minutes to hours. Type II hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement. Phagocytes and K cells may also play a role.

Treatment involves anti-inflammatory and immunosuppressive agents.

TYPE III HYPERSENSITIVITY

Type III hypersensitivity is also known as immune complex hypersensitivity. The reaction may be general (e.g., serum sickness) or may involve individual organs including skin (e.g., systemic lupus erythematosus, Arthus reaction), kidneys (e.g., lupus nephritis), lungs (e.g., aspergillosis), blood vessels (e.g., polyarteritis), joints (e.g., rheumatoid arthritis) or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms.

The reaction may take ٣ - ١٠ hours after exposure to the antigen (as in Arthus reaction). It is mediated by soluble immune complexes. They are mostly of the IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: e.g., systemic lupus erythematosus, SLE). The antigen is soluble and not attached to the organ involved. Primary components are soluble immune complexes and complement (C٣a, ٤a and ٥a). The damage is caused by platelets and neutrophils . The lesion contains primarily neutrophils and deposits of immune complexes and complement. Macrophages infiltrating in later stages may be involved in the healing process.

TYPE IV HYPERSENSITIVITY

Type IV hypersensitivity is also known as cell mediated or delayed type hypersensitivity. The classical example of this hypersensitivity is tuberculin reaction which peaks ٤٨ hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.

Table ٣ - Delayed hypersensitivity reactions

Type	Reaction time	Clinical appearance	Histology	Antigen and site
contact	٤٨-٧٢ hr	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, heavy metals, *etc.*)
tuberculin	٤٨-٧٢ hr	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, lepromin, *etc.*)
granuloma	٢١-٢٨ days	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence

				(tuberculosis, leprosy, *etc.*)

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy , chemicals, heavy metals, etc.) in which the lesions are more papular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation (Table ٣).

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH١) cells secrete cytokines which activate cytotoxic T cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage . The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-٢, interferon-gamma, TNF alpha/beta, etc.

Corticosteroids and other immunosuppressive agents are used in treatment.

Table ٥ - Comparison of Different Types of hypersensitivity

characteristics	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	exogenous	cell surface	soluble	tissues & organs
response time	١٥-٣٠ minutes	minutes-hours	٣-٨ hours	٤٨-٧٢ hours
appearance	weal & flare	lysis and necrosis	erythema and edema,	erythema and

			necrosis	induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma

Autoimmune Liver disease

Chronic active hepatitis

Chronic active hepatitis is also marked by the presence of a mononuclear cell infiltrate in the portal areas, but this also extends into the parenchyma to produce necrosis of individual periportal hepatocytes (Piecemeal necrosis).

As the disease progresses, piecemeal necrosis extends, from the portal tracts to the central veins (bridging necrosis) eventually causing cirrhosis.

Chronic active hepatitis (CAH) also has several, widely different causes:

Hepatitis B, hepatitis C, Alcohol consumption, Some medications or drugs, Some rare, inherited metabolic disorders also can lead to chronic hepatitis. They include: Wilson's disease, a condition in which the body has difficulty metabolizing copper, or Hemochromatosis, a condition of excessive iron deposits in the liver and many other parts of the body

Chronic persistent hepatitis is characterized by nonspecific inflammation of the portal zones of the liver only.

Some causes: viral hepatitis (particularly hepatitis B and hepatitis C), alcohol, drug hypersensitivity or chronic inflammatory bowel disease. In contrast to chronic active hepatitis, immunological investigations are normal, progression to cirrhosis is rare, treatment is unnecessary and the overall outlook is excellent.

In cases where no etiological agent is found, an autoimmune basis is suspected. Autoimmune hepatitis (sometimes called ‘lupoid’).

Epidemiology:

Autoimmune ('lupoid') hepatitis affects young to middle-aged women.

Many of whom (٦٠٪) have associated autoimmune disorders such as diabetes mellitus, thyroiditis and glomerulonephritis.

Signs and symptoms:

enlarged liver (hepatomegaly)

abnormal blood vessels on the skin (spider angiomas)

abdominal distention (swelling)

dark urine

pale-colored stools

yellowing of the skin and eyes (jaundice)

itching caused by a build-up of toxins and bile

fatigue, loss of appetite, nausea, vomiting, joint pain, abdominal discomfort

Etiology of autoimmune hepatitis:

Smooth-muscle antibodies (sMA): high-titer lgG antibodies to smooth muscle are classically found in autoimmune hepatitis. The target antigen is actin, a cytoskeletal protein.

Antibodies to liver and kidney microsomes (LKM): occur in a proportion of patients. The antigen recognized by LKM antibodies is a human cytochrome P٤٥٠ which shows molecular mimicry with a component of herpes simplex virus type.

An association with histocompatibility haplotypes common in autoimmune disorders (ex., HLA-B١, HLA-B٨, HLA-DR٣, HLA-DR٤).

Diagnosis:

Autoantibodies:

Actin (smooth muscle) antibody (IgG): enzyme-linked immunosorbent assay (ELISA).

ANA screen: immunofluorescence assay (IFA) with reflex to titer and pattern when screen is positive.

Liver kidney microsome (LKM-١) antibody (IgG): ELISA.

Liver biopsy:

A liver biopsy may sometimes be necessary to diagnose AIH, and can reveal the type and severity of liver damage and inflammation.

Serum protein electrophoresis and quantitative immunoglobulins:

An immunoglobulin G (IgG)-predominant polyclonal hypergammaglobulinaemia is a common finding in patients with untreated AIH.

Immunoglobulin levels typically return to normal during treatment.

Serum aminotransferases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually elevated at initial presentation.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic progressive disease characterized by progressive destruction of small intra hepatic bile ducts with portal inflammation leading to fibrosis and cirrhosis.

Epidemiology:

PBC primarily affects middle-aged women. The ratio of affected women to men has been reported to be as high as ٩:١.

Clustering of cases has also been reported, it appears that ٥٪ have affected relatives.

Signs and symptoms:

Purities (٥٠٪)

Right upper quadrant pain (٢٥٪)

Fatigue and tiredness

Jaundice (yellowing of the eyes and skin), due to increased bilirubin in the blood.

Fluid retention in the abdomen (ascites).

Etiology

The causes of primary biliary cirrhosis are unknown. Most research suggests it is an autoimmune disease. In primary biliary cirrhosis, the immune system attacks the small bile ducts in the liver.

Genetics, or inherited genes, can make a person more likely to develop primary biliary cirrhosis. Primary biliary cirrhosis is more common in people who have a parent or sibling—particularly an identical twin—with the disease. In people who are genetically more likely to develop primary biliary cirrhosis, environmental factors may trigger or worsen the disease, including:

exposure to toxic chemicals

smoking

infections

Pathogenesis (immune mechanism):

Bile ducts in PBC Patients express increased densities of adhesion molecules, MHC class II antigens; IL-٢ receptor and pyruvate dehydrogenase compared with normal ducts.

The bile duct represents potential targets for the infiltrating activated T cells (CD٤ and CD٨).

Bile duct destruction secondary to the accumulation of bile acids is thought to play a role in disease progression.

Cholestasis increases the expression of HLA class I antigens in hepatocytes in PBC.

Histology:

The characteristic histological lesion in the stages I is the presence of granulomas in the Portal tracts with destruction of middle-sized bile ducts. The damaged ducts are surrounded and infiltrated typically by CD٤ T lymphocytes, with a further surrounding infiltrate of CD٨- T cells at the periphery of the portal tract, the site at which cirrhosis develops eventually.

Stage II, there is extension of inflammation to the periportal areas.

Stage III there is formation of fibrous septa that link adjacent portal triads and bile duct loss (ductopenia). Finally, stage IV is defined by frank cirrhosis.

Diagnosis

Anti-mitochondrial antibodies (AMA) provide a vital diagnostic test. About ٩٥٪ of patients with PBC have circulating AMA by either immunofluorescence (IFA) or ELISA. The titer of AMA is greater than or equal to ١:٤٠.

Deranged liver function test (alkaline phosphatase and GGT elevated more that ALT and AST).

Abdominal ultrasound or a CT scan is usually performed to rule out blockage to the bile ducts.

١. A liver biopsy is necessary to determine the stage of disease.

Major features of autoimmune hepatitis and primary biliary cirrhosis

Feature	Autoimmune hepatitis	Primary biliary cirrhosis
Sex	Female > male (٦ : ١)	
Age at onset	١٠–٣٠ years	٤٠–٦٠ years
Associated autoimmune disease	Common	Unusual
Smooth-muscle antibodies	Positive ٨٥٪ – High titre	Not present
Antinuclear antibodies	Positive in ٨٠٪	Unusual
Anti-DNA antibodies	Often positive	Rare
Antimitochondrial antibodies	Positive ٥٪	٩٥٪
Antibodies to liver and kidney microsomes	Positive ٤٠٪ (higher in children)	
Serum immunoglobulins	IgG level raised	IgM level raised

HLA type	HLA-B٨: aggressive disease in younger patients	HLA-DR٤: extrahepatic features	None known
Response to steroids	Good		Poor
Risk of hepatoma	Low		Very Low

Primary sclerosing cholangitis (PSC)

PSC is a chronic liver disease that is characterized by chronic inflammation and fibrosis of the intra- and extra hepatic bile ducts, a cholestatic liver disease characterized by an obliterative inflammatory fibrosis of the biliary tract. It can lead to biliary cirrhosis, liver failure and carcinoma of the bile ducts.

Epidemiology:

There is a ٢:١or ٣:١ male-to-female predisposition of primary sclerosing cholangitis. The disease normally starts from age ٢٠ to ٣٠, though may begin in childhood.

Signs and symptoms: ▶

Fatigue, jaundice with intense itching/ pruritus

Malabsorption (especially of fat) and steatorrhea (fatty stool) due to biliary obstruction, leading to decreased levels of the fat-soluble vitamins, A, D, E and K.

Ascending cholangitis, or infection of the bile duct.

hepatomegaly (enlarged liver), Portal hypertension

Dark urine due to excess conjugated bilirubin, which is water soluble, being excreted by the kidneys

Hepatic encephalopathy (confusion caused by liver dysfunction).

Etiology

Genetics: Early studies described an increased frequency of HLA B٨ and DR٣ in patients with PSC.

Autoimmune disorders

Other factors

The close association between PSC and ulcerative colitis led to the hypothesis that intestinal bacteria or toxic substances might transmigrate from inflamed colonic mucosa, causing chronic inflammation and cholangitis.

The presence of bacteria and/or their toxins, and the increased concentration of potentially toxic bile acids in the portal vein may cause Kupffer cell activation to produce tumor necrosis factor (TNF)

Overproduction of TNF may ultimately result in bile duct inflammation and hepatobiliary lesions leading to portal fibrosis and PSC.

Chronic infection with cryptosporidia can also cause sclerosing cholangitis and it may be secondary to bile duct stones or bile duct surgery.

Histopathology:

The PSC staging system is similar to that used for primary biliary cirrhosis:

Stage I (portal stage) – focal inflammation limited to portal triad, with or without bile duct abnormalities, without fibrosis;

Stage II (periportal stage) – enlargement of portal tracts, periportal fibrosis with or without periportal inflammation;

Stage III (septal stage) – extension of septal or bridging fibrosis with bridging necrosis; and

Stage IV – biliary cirrhosis.

Diagnosis:

Liver function tests. These measures the activity of chemicals (enzymes) and other substances made in the liver. This gives a general guide as to whether the liver is inflamed, and how well it is working.

Other blood tests may be performed to rule out (exclude) other causes of liver conditions such as viral hepatitis.

An ultrasound scan of the liver may be performed.

A cholangiogram is a test which produces a picture of the bile ducts. This is often done using an MRI scan.

Biopsy of the liver. This may be carried out to look at the sample under the microscope. It can show inflammation and the extent of any cirrhosis (where normal liver tissue is replaced by scar tissue (fibrosis) in the liver). The liver biopsy can also assess how early or advanced the disease is.

Immunological features in primary sclerosing cholangitis

• Associated with HLA-B٨, -DR٣/-DR٥٢

• Hypergammaglobulinaemia

• Positive atypical antineutrophil cytoplasmic antibodies in ٧٠٪ of patients – associated with a more severe course

• Increased expression of HLA class II antigens on biliary epithelial cells

▶ الاختبار البعدي (Post-Test)

Q١/What are Autoimmune Liver disease

Q٢/What are Signs and symptoms

Q٣/What are Diagnosis:Autoantibodies

Q٤/ What are Autoimmune disorders

الاسبوع الرابع عشر والخامس عشر

▶ الاختبار القبلي (Pre-Test)

Q١/ What are Causes of lupus nephritis
Q٢/ What are Diagnosis of lupus nephritis

Lupus nephritis

Although only ٢٥٪ of patients with SLE present with renal disease as the first manifestation of lupus, clinical glomerulonephritis occurs in about ٥٠٪ of cases of SLE at some time, and evidence of renal involvement can be detected in most patients, even in the absence of proteinuria.

The histological appearances have been classified by the World Health Organization (WHO) according to the pattern and extent of immune deposition and inflammation (Table ١).

The prognosis in SLE is not as dismal as was once believed, but the development of renal disease is a strong predictor of ESRF (end stage renal failure) and early mortality. The ١٠-year survival in patients with all forms of the disease is over ٨٠٪. Patients with ESRF are excellent candidates for renal transplantation. Disease activity post transplantation is sporadic and infrequent; recurrence of lupus nephritis is rare.

Table ١: Modified WHO classification of lupus Nephritis

Class ٠ Normal
Class I Light microscopy normal, immune deposits on immunofluorescence involving part of a glomerulus while the rest of that glomerulus appears normal
Class II A. Mesangial deposits B. Mesangial hypercellularity
Class III Focal segmental proliferative glomerulonephritis (<٥٠٪ glomeruli) Immune deposits in mesangium
Class IV As class III but 'diffuse' (>٥٠٪ glomeruli) Includes membranoproliferative type
Class V Membranous nephropathy with subepithelial immune complex deposition A. Membranous nephropathy (MN) alone B. MN plus class II C. MN plus class III D. MN plus class IV
Class VI Glomerulosclerosis

Causes of lupus nephritis

١. Genetic predisposition mainly in HLA DR٢ & DR٣ people

٢. Complement genetic defect (C١q, C٢ & C٤)
٣. Genetic defect in cytokines genes mainly IL١, IL ١٠ & TNF genes
٤. Mannose binding lectin genes defect MBL
٥. Apoptosis gene defect

Diagnosis of lupus nephritis

١. Kidney biopsy to see the pattern of distribution of ICs
٢. X- ray, ultrasound, GUE, blood tests
٣. Evaluating renal function:
a. Blood urea nitrogen
b. Serum creatinine
c. GUE to check protein, RBCs, casts
٤. Tests for SLE activity
a. Anti-ds DNA
b. Complement activity (C٣, C٤)
c. CRP, ESR

Pathogenesis:

Immune complex deposits in the glomeruli are primarily responsible for the inflammatory process that causes glomerular damage. If deposited in the mesangium and subendothelial space, immune complexes will activate the complement (cause hypocomplementemia) and generate chemo-attractants (C٣a and C٥a). The result is an influx of neutrophils and mononuclear cells that secrete proteases, reactive oxygen species, and cytokines, causing glomerular injury.

Glomerular thrombosis is another mechanism that may play a role in pathogenesis of lupus nephritis, mainly in patients with antiphospholipid antibody syndrome, and is believed to be the result of antibodies directed against negatively charged phospholipid-protein complexes.

Immune complexes identified in lupus nephritis include:

١. DNA-anti-DNA
٢. nucleosomes, chromatin
٣. C١q
٤. Laminin

٥. Sm La (SS-B) and Ro (SS-A)

٦. Ribosomes.

Signs and symptoms:

The first noticeable symptom is swelling of the legs, ankles and feet. Less often, there can be swelling in the face or hands.

Other symptoms can vary from person to person and from day to day. They may include:

١. Weight gain, High blood pressure

٢. Dark urine, Foamy, frothy urine

٣. The need to urinate during the night

Treatment

- Systematic review of available trials supports treatment with corticosteroids and an immunosuppressive agent, usually cyclophosphamide or azathioprine.
- A Cochrane review showed that cyclophosphamide plus steroids slowed progression to ESRF but had no impact on mortality and with a significant risk of ovarian failure.
- Azathioprine plus steroids reduced the risk of mortality but did not alter renal outcomes.
- Ciclosporin is an alternative agent, particularly used in children to reduce corticosteroid complications.

Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) describes a group of diseases with aggressive glomerular injury that can lead to severe renal failure within days or weeks if not diagnosed and treated early.

The usual pathological lesion is crescentic glomerulonephritis. RPGN constitutes ٣–٥٪ of all cases of glomerulonephritis.

It has multiple etiologies involving several pathogenic mechanisms. Based on the immunological findings, patients fall into three broad groups, as shown in Figure ١ below.

The prognosis is especially grave when over ٧٠٪ of glomeruli are involved, there are diffuse circumferential crescents and there is prolonged oliguria.

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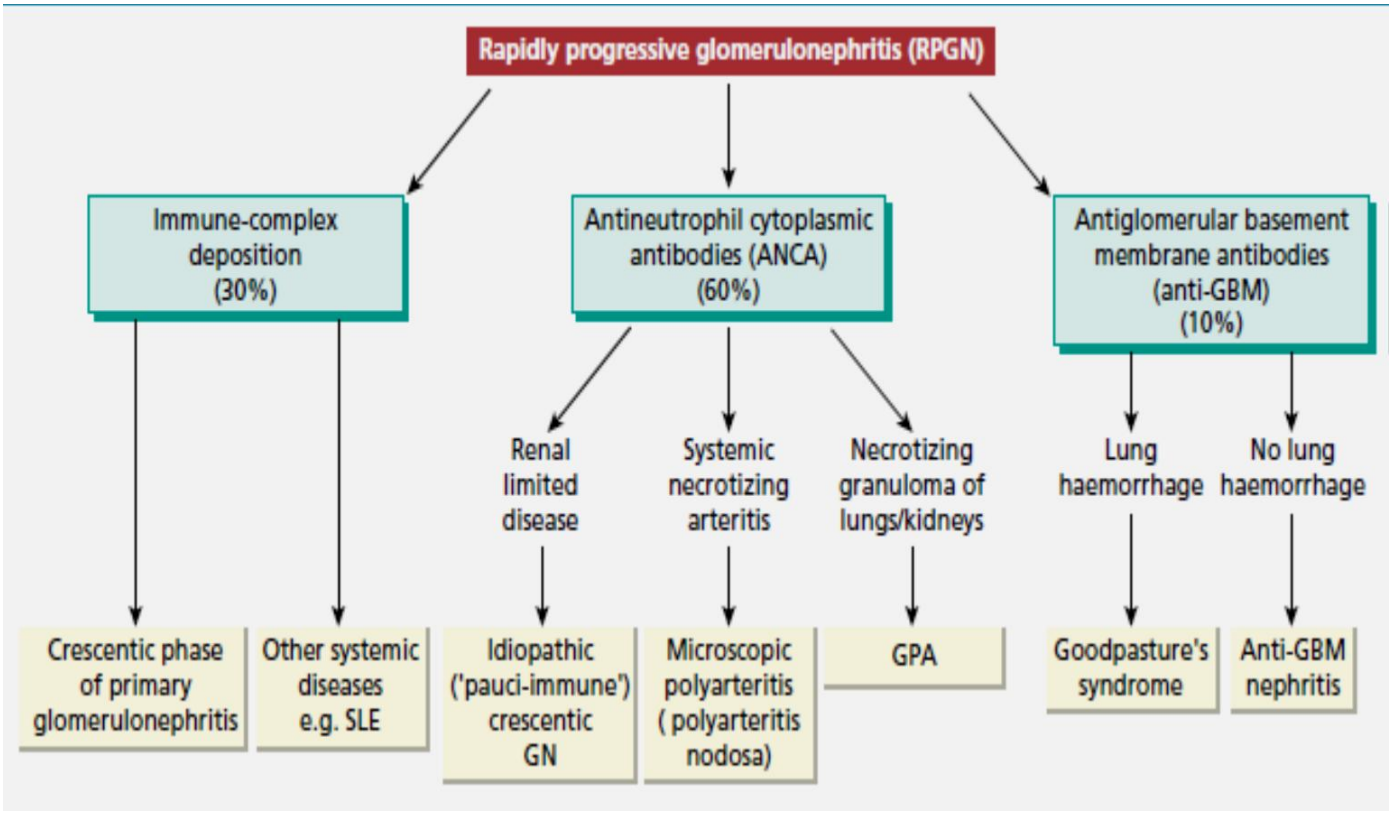


fig.١: Clinical and immunological classification of rapidly progressive glomerulonephritis.

A. Anti-glomerular basement membrane disease

Acute glomerulonephritis mediated by anti-GBM antibody accounts for about ١–٢٪ of all cases of glomerulonephritis, but about ٢٠٪ of cases presenting as acute renal failure due to RPGN.

Anti-GBM nephritis is more common in those who possess HLA-DR١٥ or -DR٤, and less common in those with DR١ or DR٧.

Patients present with nephritis alone or commonly with glomerulonephritis and lung haemorrhage, a combination termed Good pasture's syndrome.

However, rapidly progressive nephritis and pulmonary haemorrhage can occur in other multisystem disorders such as SLE or granulomatosis with polyangiitis

(GPA), so *the combination of renal and lung involvement is not synonymous with anti-GBM disease*.

The target antigen is the α٣ chain of type IV collagen, a major constituent of the GBM. Lung damage results from antibodies to antigens common to both alveolar and glomerular basement membranes.

In Goodpasture's syndrome, respiratory symptoms often precede renal disease by ١ year or longer.

Haemoptysis, sometimes severe enough to cause anaemia, is a prominent feature and the sputum typically contains haemosiderin-laden macrophages. Lung biopsies show intraalveolar haemorrhage and necrotizing alveolitis.

Renal biopsy reveals crescenteric glomerulonephritis with linear deposition of IgG along the glomerular capillaries.

Although the trigger is unknown, anti-GBM disease follows upper respiratory tract infections in ٢٠–٦٠٪ of patients, or exposure to certain hydrocarbons as in smoking. These agents may damage alveolar basement membrane, generating new, previously hidden ('cryptic') and potent antigens that are highly susceptible in antigen processing by endosomal proteases and so able to stimulate autoantibody production. Pulmonary haemorrhage in anti-GBM disease is strongly associated with cigarette smoking. Experimental data implicate both autoantibodies and cell-mediated immunity in pathogenesis, and there are reports that T regs are increased in the convalescent phase.

The prognosis of anti-GBM disease is extremely poor, without appropriate treatment the likelihood of requiring dialysis or dying from the disease is over ٩٠٪.

B. Antineutrophil cytoplasmic antibody-associate glomerulonephritis (ANCA)

Serum IgG antibodies reacting with cytoplasmic components of neutrophils and monocytes are a diagnostic marker for active granulomatosis with polyangiitis (formerly Wegener's granulomatosis) and reflect disease activity.

There are many evidence for role of ANCA in these dz.:

١. Wegener's granulomatosis
٢. Microscopic polyangiitis
٣. Churg-Strauss Vasculitis

There are two types of antineutrophil cytoplasmic antibody (ANCA) reactivity are important clinically:

١. Generalized cytoplasmic staining (cANCA): most cANCA sera react with a serine proteinase called proteinase ٣ (PR٣).
٢. Perinuclear pattern (pANCA): most pANCA sera react with myeloperoxidase (MPO).

A further pattern is associated with inflammatory bowel disease, particularly ulcerative colitis.

Some cANCA/pANCA positive sera react with neutrophil antigens other than PR٣/ MPO, particularly after infections.

Raised ANCA titres are generally detectable during active granulomatosis with polyangiitis, and rising titres may herald a relapse. There has been debate whether ANCAs are pathogenic in vasculitis or simply a marker, but there is mounting evidence that they are pathogenic.

The exact pathogenesis of granulomatosis with polyangiitis is not completely understood, but T cells, B cells, neutrophils and endothelial cells have all been implicated in the process.

Patients with ANCA-associated glomerulonephritis are usually aged from ٤٠ to ٧٠ years and most have had a flu-like illness with arthralgia and myalgia a few days or weeks prior to the onset of renal disease or vasculitis.

A spectrum of vasculitis is seen, ranging from disease limited to the kidneys in about ٢٥٪ of cases to a systemic vasculitic process with pulmonary involvement in ٥٠٪.

ANCA-associated glomerulonephritis is now the commonest form of crescentic or RPGN.

The renal lesion in characterized by few or no deposits of immunoglobulin or complement in the kidney (so-called pauci-immune glomerulonephritis) and by necrosis and crescent formation.

Over ٧٥٪ of patients with ANCA-associated glomerulonephritis go into remission following aggressive immunosuppression, although ٣٠–٥٠٪ relapse within ٢ years and require further therapy.

Treatment

Aggressive immunosuppressive therapy, a usually high-dose steroid combined with cyclophosphamide

Intensive plasmapheresis, is the treatment of choice.

Membranous glomerulonephritis

About ٨٠٪ of patients with membranous glomerulonephritis present with a florid nephrotic syndrome; the remainder present with hypertension, poorly selective proteinuria or microscopic haematuria discovered on routine examination of the urine.

Membranous glomerulonephritis can occur at any age, with the peak incidence in adults aged between ٤٠ and ٧٠ years.

The characteristic lesion is uniform thickening of the GBM without proliferation of cells. The lesions uniformly affect every glomerulus, but the degree of membranous thickening is not related to the severity of proteinuria.

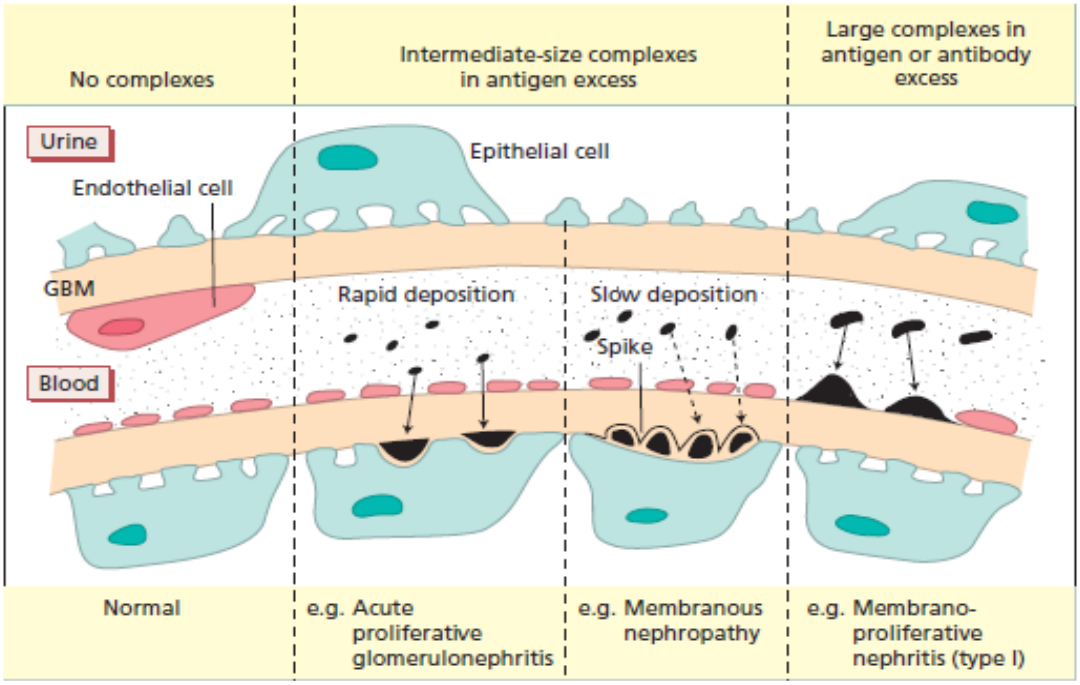
The membranous thickening is produced mainly by subepithelial deposits of immune complexes, followed by secondary formation of projections (‘spikes’) of basement membrane material between the deposits as illustrated in fig.١.

The deposits are characteristically granular and may contain C٣, IgA and IgM as well as IgG. About ٨٠٪ of cases of membranous glomerulonephritis are

primary, i.e. no known cause has been found. The remaining ٢٠٪ of cases are secondary to another disease or to drugs.

The most important causes are drugs [gold, penicillamine, non-steroidal anti-inflammatory drugs (NSAIDs), captopril, heroin], infections (hepatitis B or C, malaria, syphilis), SLE or tumours (carcinoma of the bronchus, breast or colon).

There is considerable evidence that the pathogenesis of membranous nephropathy is immunologically mediated. There is increasing evidence that complexes are formed in situ in the subepithelial space. Recently, the identification of several target antigens in human podocytes has led to the finding of specific autoantibodies, though their pathogenic role is as yet uncertain. A genome-wide association study has provided further evidence for a lphighly significant association between a gene for one such antigen (PLA٢R١) and HLADQA١



▶ الاختبار البعدي (Post-Test)

Q١/ Enumarate WHO classification of lupus Nephritis

Q٢/ What are types of antineutrophil cytoplasmic antibody (ANCA) reactivity are important clinically

Q٣/ What are Anti-glomerular basement membrane disease

Q٤/ What are types of antineutrophil cytoplasmic antibody (ANCA) reactivity are important clinically:

Q٥/ What are Membranous glomerulonephritis

المصادر الاساسية:

-Müller, W. E., B. Blumbach, and I. M. Müller. ١٩٩٩. "Evolution of the Innate and Adaptive Immune Systems: Relationships between Potential Immune Molecules in the Lowest Metazoan Phylum (Porifera) and Those in Vertebrates."

-Murphy, Kenneth, and Casey Weaver. ٢٠١٦. *Janeway's Immunobiology*. ٩th edition. New York, NY: Garland Science/Taylor & Francis Group, LLC.

-Randow, Felix, John D. MacMicking, and Leo C. James. ٢٠١٣. "Cellular Self-Defense: How Cell-Autonomous Immunity Protects Against Pathogens." *Science (New York, N.Y.)* ٣٤٠ (

-Delves, P. J. (٢٠٢٠, April). Overview of the Immune System. Retrieved January ١٣, ٢٠٢١, from https://www.merckmanuals.com/home/immunedisorders/biology-of-the-immune-system/overview-of-the-immune-system ١٨. --

-Tao, X., & Xu, A. (Eds.). (٢٠١٦). Basic Knowledge of Immunology. Amphioxus Immunity, ١٥-٤٢. https://doi.org/١٠,١٠١٦/B٩٧٨-٠-١٢-٨٤٩٩٠٣-٠,٠٠٠٠٢-٦

روابط مقترحة ذات صلة :

- -https://www.slideshare.net/slideshow/immunodiffusion-٢٤٧٤٩١٩٤٥/٢٤٧٤٩١٩٤٥
- https://www.google.com/search?q=Radioimmunoassay&oq=Radioimmunoassay&gs_lcrp=EgZjaHJvbWUyBggAEEUYOTIHCAEQABiABDIHCAIQABiABDIHCAMQABiABDIHCAQQABiABDIHCAUQABiABDIHCAYQABiABDIGCAcQABgeMgYICBAAGB٤yBggJEAAYHtIBCDExMjdqMGo٠qAIAsAIA&sourceid=chrome&ie=UTF٨#fpstate=ive&vld=cid:٠c٤٦e٥١٧,vid:JtbcqkiFf٧w,st:٠
- -https://www.creativebiolabs.net/radioimmunoassay.htm
- https://www.healthline.com/health/vdrl-test
- - https://www.arthritis.org/diseases/rheumatoid-arthritis
- https://www.webmd.com/a-to-z-guides/autoimmune-diseases
- https://www.mayoclinic.org/diseases-conditions/lupus-nephritis/symptoms-causes/syc-٢٠٣٥٤٣٣٥