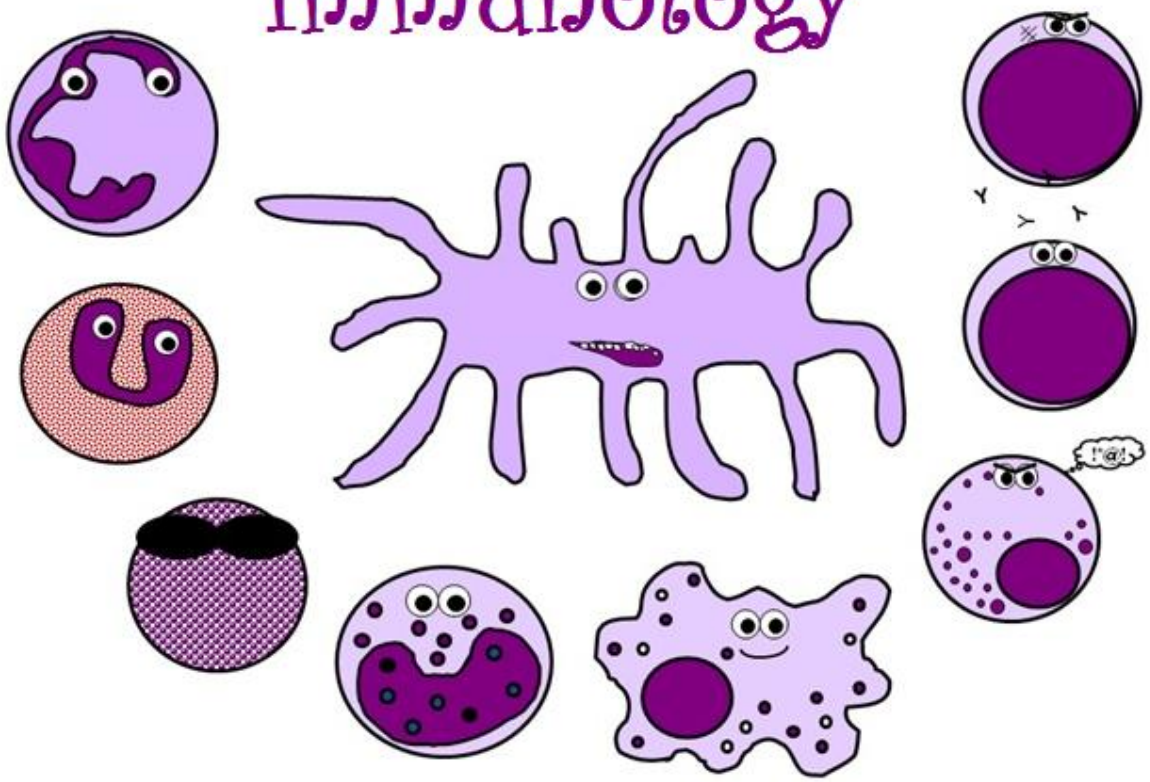
Immunology



◉Sheet ○Slides

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Subject: Dr. Mohammad Al-Tamimi notes

Done by: Mohammad Qussay Al-Sabbagh

Doctor: Mohammad Al-Tamimi

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Before we start ..

●Hi all, as we know, this course has been given by two doctors; Dr. Issa and Dr. Mohammad. And it's impossible to study two different sources before any exam. So I tried to collect any peace of information that's mentioned by Dr. Mohammad but not Dr. Issa in this sheet.

●The best way to study any lecture is by studying and understanding Dr. Issa sheet, then go over corresponding notes for each lecture separately.

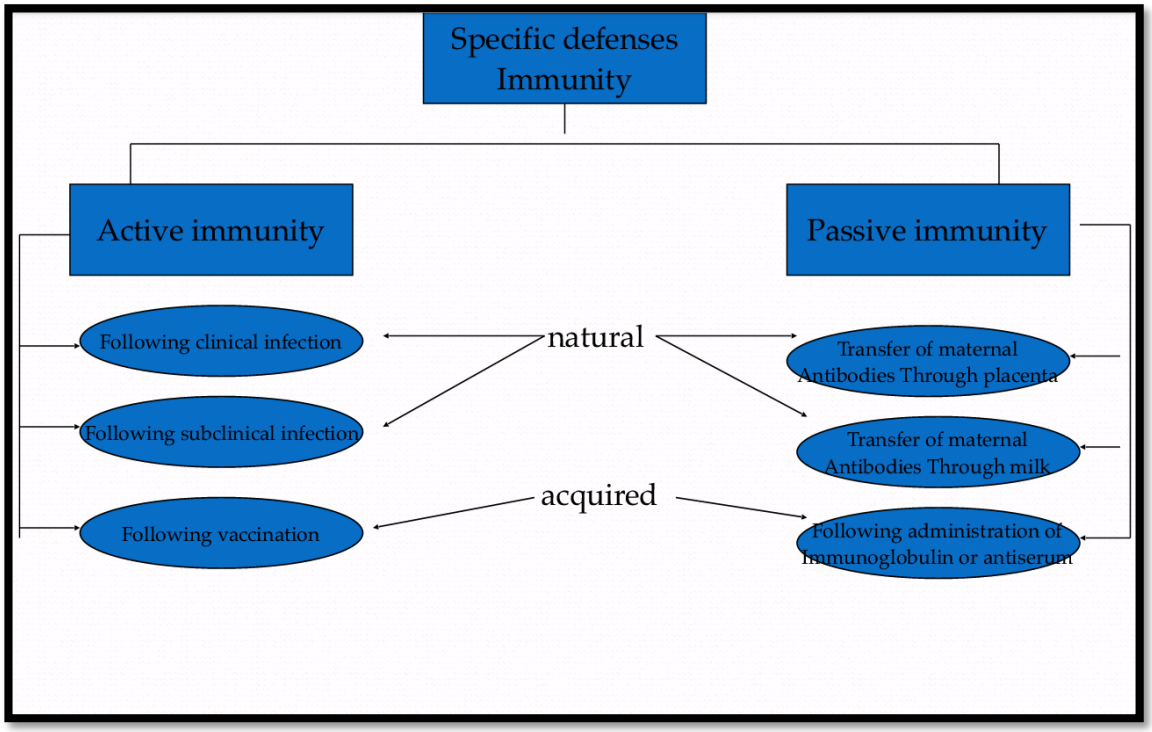
●For those how are قطاعات أكثر من اللازم and want to study Dr. Mohammad slides also, I did a simple cross-matching between Dr. Issa and Dr. Mohammad lectures.

Dr. Issa	Dr. Mohammad
Lec.15	Slide14 (Immunization)
Lec.16	Slide9 (Autoimmunity)+Slide10 (Hypersensitivity Reactions)
Lec.22	Slide12 (Immune Deficient Diseases)+ Slide13 (HIV)
Lec.24	Slide11 Tumour Immunology
Lec.25	-

Lec.15 Immunological Memory & Vaccines:

●***Active immunity***: Resistance developed in response to stimulus by an antigen (infecting agent or vaccine) and is characterized by the production of antibodies by the host. ***It's the goal of vaccination, and it's better than passive immunity as it gives live-long immunity.***

●***Passive immunity:*** Immunity conferred by an antibody produced in another host. It may be acquired naturally or artificially (through an antibody-containing preparation).



● Immunizing agents are:

1) ***Antisera***: These are materials prepared in animals or non human sources such as horses.
2) ***Immunoglobulins***: Two types of immunoglobulin preparations are available for passive immunization; Normal human immunoglobulin and Specific (hyper-immune) human immunoglobulin
3) ***Vaccines***

●Types of vaccines:

- ***Live vaccines***: made from live infectious agents, not used anymore. Eg: *"Variola" small pox vaccine*,

- ***Attenuated live vaccines:***
  #Note: ***Live attenuated vaccines should be avoided in: Leukemia and lymphoma, Other malignancies, Receiving corticosteroids and anti-metabolic agents, Radiation and Pregnancy***
- ***Killed Vaccines:***

1. Inactivated (killed vaccines): only absolute contraindication to their administration is a severe local or general reaction to a previous dose.
2. Toxoids: They are prepared by detoxifying the exotoxins of some bacteria rendering them antigenic but not pathogenic. Adjuvant (e.g. aluminum precipitation) is used to increase the potency of vaccine.
3. Polysaccharide and polypeptide (cellular fraction)

- ***Surface antigen (recombinant) vaccines***.

●***Conjugate vaccines:*** A conjugate vaccine is created by covalently attaching a (polysaccharide organism) antigen to a carrier protein (preferably from the same microorganism), thereby conferring the immunological attributes of the carrier on the attached antigen. This technique for the creation of an effective immunogen is most often applied to bacterial polysaccharides. Sometimes it's used to mix more than one vaccine (MMR or DTP).

●You have to be familiar with this table, especially live attenuated vaccines.

Live vaccines	Live Attenuated vaccines	Killed Inactivated vaccines	Toxoids	Cellular fraction vaccines	Recombinant vaccines
•Small pox variola vaccine	•BCG •Typhoid oral •Plague •Oral polio •Yellow fever •Measles •Mumps •Rubella •Intranasal Influenza •Typhus	•Typhoid •Cholera •Pertussis •Plague •Rabies •Salk polio •Intra-muscular influenza •Japanise encephalitis	•Diphtheria •Tetanus	•Meningococcal polysaccharide vaccine •Pneumococcal polysaccharide vaccine •Hepatitis B polypeptide vaccine	•Hepatitis B vaccine

●**Routes of administration:**

- Deep subcutaneous or intramuscular route (most vaccines)
- Oral route (sabine vaccine, oral BCG vaccine)
- Intradermal route (BCG vaccine)
- Scarification (small pox vaccine)
- Intranasal route (live attenuated influenza vaccine)
- Notice that we never give IV vaccines !

●Primary vaccination:

- One dose vaccines (BCG, variola, measles, mumps, rubella, yellow fever)
- Multiple dose vaccines (polio, DPT, hepatitis B)

●Booster vaccination: To maintain immunity level after it declines after some time has elapsed (DT, MMR).

●**Periods of maintained immunity due to vaccines:**

- Short period (months): cholera vaccine
- Two years: TAB vaccine
- Three to five years: DPT vaccine
- Five or more years: BCG vaccine
- Ten years: yellow fever vaccine
- Solid immunity: measles, mumps, and rubella vaccines.

●**Levels of effectiveness:**

- Absolutely protective(100%): yellow fever vaccine
- Almost absolutely protective (99%): Variola, measles, mumps, rubella vaccines, and diphtheria and tetanus toxoids.
- Highly protective (80-95%): polio, BCG, Hepatitis B, and pertussis vaccines.
- Moderately protective (40-60%) TAB, cholera vaccine, and influenza killed vaccine.

●***Hazards of Immunization:***

- Reactions inherent to inoculation: local and general
- Reactions due to faulty techniques: during manufacturing or giving of vaccine
- Reactions due to hypersensitivity

- Neurological involvement: GuillainBarre syndrome in association with the swine influenza vaccine
- Provocative reactions: occurrence of new disease not connected to the vaccine.

Lec.15 immune system going wrong:

●Autoimmune disease Can be classified into clusters that are either organ-specific or systemic.

●Remember that each autoimmune disease requires three factors; **genetic**, **environmental** and **loss of tolerance**.

- Examples of **genetic factors**: NOD2: polymorphism associated with ~25% of Crohn's disease/ PTPN22: polymorphism in RA,SLE.

●**environmental factors** are: Pathogens, drugs, hormones, and toxins are just a few ways that the environment can trigger autoimmunity:

- **Drugs**: Drug induced lupus
- **Toxins**: Toxic Oil Syndrome(Occurred in Spain in 1981 after people ate contaminated olive oil/ People developed unique illness marked by lung disease, eosinophilia, and excessive IgE.
- **Hormones**: Females are much more likely to develop autoimmune illness (Hypothesis: estrogen response elements (EREs) in several genes).

● The nature of the disease is determined by the type of dominant immune response:

- ***Th1 response***: inflammation, autoantibody production; autoimmune diseases
- ***Th2 response***: IgE+eosinophil-mediated inflammation; allergic reactions
- ***Th17 response:*** acute or chronic inflammation; increasingly recognized in immune-mediated diseases.

●examples of autoimmune disease:

- ***Hashemot's thyroiditis***: Individual produce autoantibodies and sensitize Th1 cells specific for thyroid antigen→Antibodies re formed against thyroid proteins including thyroglobulin and thyroid peroxidase → Binding of these antibodies to these proteins interferes with iodine uptake leading to hypothyroidism → Intense infiltration of thyroid gland with lymphocytes,

macrophages, and plasma cells →Inflammatory response leads to goiter and hypothyroidism.

- ***Autoimmune anemias:*** It includes ***pernicious anemia*** (caused by antibodies to intrinsic factors on gastric parietal cells which blocks vit B12 absorption necessary for hematopoiesis), ***autoimmune hemolytic anemia*** (results from autoantibodies to RBCs → antigens triggering complement mediated lysis or antibody mediated opsonization and phagocytosis) and ***drug induced hemolytic anemia*** (Certain drugs like penicillin or methyldopa induce hemolysis of RBCs).
- ***Goodpastuare's syndrome***: Autoantibodies specific for basement membrane antigens of kidney glomeruli and alveoli → Complement activation and inflammatory response induce cellular damage leading to progressive kidney damage and lung hemorrhage.
- Other autoimmune diseases are discussed in Dr. Issa lectures + Case study.

● ***Hypersensitivity reactions***: 'over reaction' of the immune system to harmless environmental antigens:

- Hypersensitivity refers to 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.
- Allergen: the antigens that give rise to immediate hypersensitivity.

● There are 4 types of hypersensitivity reactions:

- Type I: classical immediate hypersensitivity (IgE mediated/ Atopy/ allergy
- Type II: cytotoxic hypersensitivity
- Type III: immune-complex mediated hypersensitivity
- Type IV: cell mediated or delayed hypersensitivity
- Types I, II and III are antibody mediated
- Type IV is cell mediated

●pathogenesis and definition of Type 1 hypersensitivity were discussed in case study lectures (Allergic asthma and anaphylaxis) .

● Type II: Cytotoxic or Cytolytic Reactions

- An antibody (IgG or IgM) reacts with antigen on the cell surface, This antigen may be part of cell membrane or circulating antigen (or hapten) that attaches to cell membrane.

- Cell lysis results due to :
  1.***Complement fixation*** to antigen antibody complex on cell surface. The activated complement will lead to cell lysis.
  2.Phagocytosis is enhanced by the antibody (opsinin) bound to cell antigen leading to opsonization of the target cell
  3. ***Antibody depended cellular cytotoxicity*** (ADCC): Antibody coated cells: e.g. tumour cells, graft cells or infected cells can be killed by cells possess Fc receptors, The process different from phagocytosis and independent of complement. Cells most active in ADCC are: ***NK, macrophages, neutrophils and eosinophils.***

●examples of type II:

- Transfusion reaction due to ABO incompatibility
- Rh-incompatibility (Hemolytic disease of the newborn)
- Autoimmune diseases: The mechanism of tissue damage is cytotoxic reactions e.g. SLE, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, myasthenia gravis, nephrotoxic nephritis, Hashimoto's thyroiditis.
- **A non-cytotoxic Type II hypersensitivity is Graves's disease**. It is a form of thyroiditis in which antibodies are produced against TSH surface receptor →This lead to mimic the effect of TSH and stimulate cells to over- produce thyroid hormones.
- Graft rejection cytotoxic reactions: In hyperacute rejection the recipient already has performed antibody against the graft
- Drug reaction (type II): Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to hemolysis. Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura.

● Type III: Immune Complex Mediated Reaction (discussed in SLE case study), another example is:

- ***Arthus Reaction***: is a local immune complex deposition phenomenon e.g. diabetic patients receiving insulin subcutaneously→ Local reactions in the form of edema erythema necrosis → Immune complexes deposited in small blood vessels →vasculitis, microthrombi formation, vascular occlusion and necrosis.

• Type IV: Cell Mediated delayed Type Hypersensitivity T-cells cause tissue injury by directly killing target cells by CD8 or by triggering DTH reactions by TH1

- TH1 and CD8 T cells secrete cytokines (IFN-γ and TNF) Cytokines → attract lymphocytes → activate macrophages→induce inflammation →Tissue damage results from products of activated macrophages.
- Caused by products of antigen-specific effector T cells
- T cells undergo blastogenesis and cellular division production of reactive cells
- No histamine or chemically related substances are released from cells
- The classical example of this hypersensitivity is ***tuberculin test*** which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.
- ***Granulomatous lesions In chronic diseases*** : TB, Leprosy, schistosomiases. Intracellular organisms resist destruction by macrophage → Persistent antigen in tissues stimulate local DTH reaction → Continuous release of cytokines leads to accumulation of macrophages which give rise to epitheloidal and giant cell granuloma.
- ***Contact Dermatitis***: Contact of skin with chemical substances or drugs e.g. poison, hair dyes, cosmetics, soaps, neomycin→ These substances enter skin in small molecules → They are haptens that attached to body proteins, form immunogenic substances → DTH reaction to these immunogenic subst. lead to inflammatory reaction of skin in (eczema, rash or vesicular eruption).

Lec. 22 Immunodeficiency

1. B-cell defect

●Causative agents are most commonly extracellular organisms, namely pyogenic and enteric bacteria, because patients are deficient in serum antibodies necessary for phagocytosis.

- Recurrent infections with encapsulated bacteria
- Chronic sinupulmonary infections
- Sites of infection include the skin, sinuses, meninges, and the respiratory, urinary, and gastrointestinal tracts.

A. Bruton's Agammaglobulinemia

●Immunology:

- No B cells or non functional B cells including defective signaling or defective BCR.
- Markedly low levels of Immunoglubulines

●Clinical:

- Child clinically well for first 6 months of life
- Recurrent upper/lower respiratory tract infections with encapsulated bacteria (S. pneumonia) Sepsis, meningitis, skin infections
- Short life span
- Treatment: IVIG, antibiotic therapy.

B. IgA deficiency

●Immunology:

- Most common humoral antibody deficiency
- Isolated low IgA level

●Manifestation:

- 50-80% asymptomatic
- Recurrent sinopulmonary infections most frequent manifestation
- May have severe malabsorption (chronic diarrhea)
- Increased risk of autoimmune disorders
- Treatment: Broad spectrum antibiotics

2. T-cell deficiency disorders

●Also known as cell-mediated (cellular) immunodeficiencies, result from abnormalities in T-cell functions.

●Antibody production is also likely to be affected in patients with severe T-cell abnormalities because T cells are important immunoregulators of B-cell differentiation and function.

●Recurrent infections ,Causative agents are intracellular pathogens (e.g., herpesviruses, mycobacteria, fungi (Candida), and protozoa (Pneumocystis carinii, Toxoplasma).

●the only required example is DiGeorge syndrome, discussed in dr. Issa lecture.

- Note: DiGeorge syndrome arise from failure to form 3rd and 4th pharyngeal pouches, so it's associated also with hypPTH and cardiac defects → patients will develop hypocalcemia.

3. Combined Deficiencies

●Immunological abnormalities are combined to B cells and T cells.

● Immunology:

- Defects in stem cell maturation with various genetic defects
- No TCR or defective TCR
- Defective cell signaling
- Defective IL 2
- Manifestations seen in first 3 months of life
- Recurrent, severe bacterial, viral, fungal, and protozoan infections (usually respiratory infections)
- Failure to thrive, diarrhea, dermatitis, candidiasis ! Death at early age
- Treatment: isolation, treat underlying infections, bone marrow transplant.

●Example: Wiskott Aldrich Syndrome

- X linked disorder
- Affects platelet numbers/function
- Affects T cell function
- Cytoskeleton of lymphocytes affected
- Lower amounts of IgM
- Symptoms in infancy: Recurrent, severe infections, Eczema, Thrombocytopenia (petechiae)
- Treatment: manage bleeding/infections, BMT.

4. Phagocyte disorders

●Clinical features: Affected individuals are prone to infections with low-grade bacteria such as Staphylococcus aureus and gram-negative enteric bacteria.

●example: Chronic Granulamatous Disease (CGD)

- Non functional phagocytes
- Defective NADPH oxidase
- 75% X-linked recessive, 25% autosomal recessive
- Manifestation: Severe, recurrent staph aureus infections of lymph nodes, skin, and lung
- Dx: Nitroblue tetrazolium (NBT) test
- treatment: antimicrobial prophylaxis, IFN-gamma, BMT.

5. Complement Disorders

●Deficiency of early complement components (C1, C4, C2) results in a symptom complex resembling collagen vascular disorders (e.g., systemic lupus erythematosus (SLE)] and increased susceptibility to pyogenic infections.

●C3 deficiency results in severe pyogenic infections. Several patients have also had SLE and glomerulonephritis.

●Deficiency of late complement components (C5, C6, C7, C8) results in systemic Neisseria infections such as meningococcal sepsis and meningitis, and disseminated gonococcal infections.

6. Diagnosis of immunodeficiency disease

●laboratory investigation:

- CBC: increase PMNL suspect phagocyte deficiency
- Culture: to know the organism and choose the antibiotics.
- ESR and CRP: inflammation markers for follow up.

●Specific tests:

- B-cells: Total lg, Selected lgA and lgG, Anti A and Anti B Antibodies for pervious vaccination
- T cells: Lymphocyte count, Delayed hypersensitivity reaction, T cells and macrophage function test.
- Phagocyte: Neutrophil count, NBT test for screening, Macrophage function test
- Complement: Total and specific complement count.

●***AIDS***: what's discussed in dr. Issa lecture + the related case is enough.

Lec. 24 Cancer and The Immune System

● Tumor Associated Antigens:

- Viral Antigen: Viral proteins and glycoproteins, New antigens produced by virally infected host cells under control of viral nucleic acid
- Tumor specific antigens: Tumor cells develop new antigen specific to their carcinogen
- Tumor specific transplantation antigens: Tumor cells express new MHC antigens due to alteration of normally present MHC antigens
- Oncofetal antigens:

1. Carcino-embryonic antigens (CEA) Normally expressed during fetal life on fetal gut Reappearance in adult life: GIT, pancreas, biliary system and cancer breast
2. Alpha fetoprotein: Normally expressed in fetal life Reappearance in adult life; hepatoma.

● Evidence for Immune Reactivity to Tumors:

- Tumors that have severe lympho -reticular infiltration have a better prognosis than those that do not.
- Certain tumors regress spontaneously. This is the only Scientific explanation for regression of tumors in some stories
  (شخص مصاب بسرطان خطير، بعد الصلاة أو الذهاب إلى الحج أو الدعاء اختفى ذلك السرطان)
- There is an increased incidence of primary and secondary malignancies (particularly lympho-reticular tumors) in immunodeficient patients
- Antibodies and immune T lymphocytes have been detected in patients with tumors.
- The young and the very old have an increased occurrence of tumors.
- Finally, animals can be specifically immunized against various types of tumors.

●Mechanisms by which tumor escape immune defenses:

- Reduced levels or absence of MHCI molecule on tumor so that they can not be recognized by CTLs.
- Some tumors stop expressing the antigens These tumors are called “antigen loss variants”
- Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF-β)

- Tumor antigens may induce specific immunologic tolerance.
- Tumor cells have an inherent defect in antigen processing and presentation
- blocking of receptors on T-cells by specific antigen antibodies complex (after shedding of tumor Ag) prevents them from recognizing and attacking tumor cells
- Antigens on the surface of tumors may be masked by sialic acid-containing mucopolysaccharides
- Immune suppression of the host as in transplant patients who show a higher incidence of malignancy.

● Tumor Markers

- Tumor markers are either ***Tumor antigens*** or ***Tumor products*** (enzymes and hormones)
- Tumor products are released in the serum of patients
- They are used to confirm diagnosis and follow up the response to therapy.

● Tumor Antigens:

- Alpha fetoprotein antigen (AFP) → hepatoma
- Carcinoembryoinic antigen (CEA) → gastrointestinal tumors, tumors of biliary system and cancer breast
- Cancer antigen 125 (CA 125) → ovarian carcinoma
- Cancer antigen 15-3 (CA15-3) → breast cancer
- Cancer antigen 19-9 → colon and pancreatic tumor
- Prostatic specific antigen (PSA) → prostatic tumors

● Tumor Products:

- Hormones: Human chorionic gonadotrophins (HCG) are secreted in cases of choriocarcinoma / Thyroxin (T3 & T4) is secreted in cases of cancer of thyroid gland
- Enzymes: Acid phosphatase enzymes in cases of cancer prostate /Alkaline phosphatese, lipase and amylase enzymes in cases of cancer pancreas.

●Applications of Tumor Immunology: ***Diagnosis*** (other applications are discussed in Dr, issa lectures.

- Monoclonal antibodies labeled with radioisotope have been used for in vivo detection of relatively small tumor foci.
- Antibodies have also been used in vitro to identify the cell origin of undifferentiated tumors, particularly of lymphocytic origin.
- Immuno-histological staining is used to confirm suspected metastatic foci, especially in bone marrow.

And by that, you have covered all the material … your max is waiting :p

Good luck in you exams قطاعاتنا