





Tumor Markers

BY

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INTRODUCTION

- **Cancer** is a word used to describe a condition characterized by spreading destruction of any kind.
- **Cancer** is a group of diseases associated with the development, growth, and spread of destructive overgrowths of tissue, called, *malignant tumor or neoplasm*, in living organism.

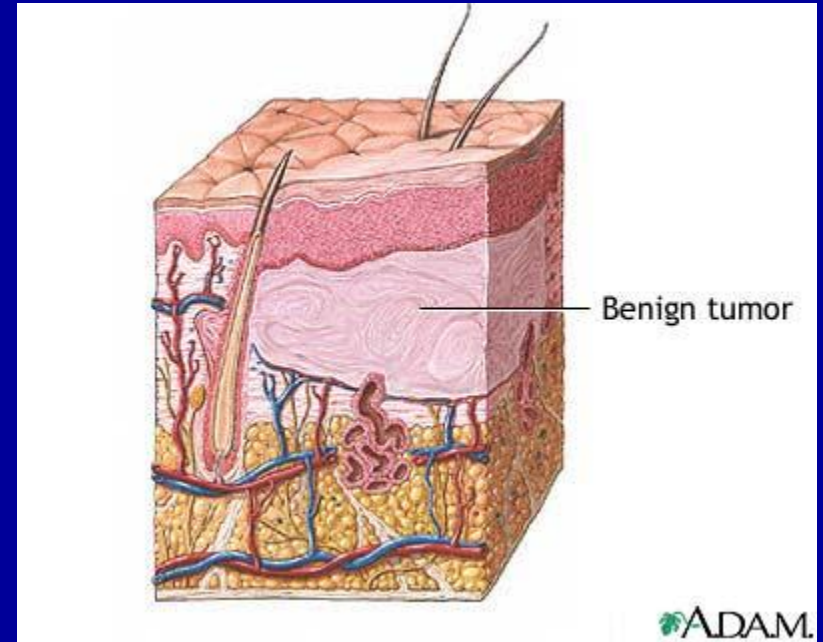
- A tumor is *benign* when it is restricted to its primary site.
- A tumor is *malignant* when it is capable of invading surrounding tissue

ONCOLOGY

- Study and treatment of tumors
- **TUMORS:**
 - Proliferation of cells that produce a mass
 - **Neoplasm** : Benign or Malignant

BENIGN

- Well-differentiated
- Slow growth
- Encapsulated
- Non-invasive
- Does NOT metastasize



MALIGNANT

- Undifferentiated
- Erratic and Uncontrolled Growth
- Expansive and Invasive
- Secretes abnormal proteins
- Metastasizes



Malignant tumors

- These are invasive, destructive and associated with a generally poor prognosis and high mortality rate. Malignant tumor growth may occur at any site in the organism and may spread in time to other sites.

Pathogenesis of the disease is largely due to:

- A. Obstruction and destruction of other vital structures in the body.
 - B. Functional activity of a substance produced by the tumor.
 - C. Bleeding.
 - D. Infection.
 - E. Toxic substances associated with infarction and necrosis.
- The major difference between normal cells and tumor cells is that growth control has been lost in tumor cells.

➤ Neoplastic transformation is associated with altered gene expression, which may affect production of enzymes, hormones, receptors, proteins, and metabolites that are released into the circulatory system.

➤ These substances, if they can be measured, and in the **diagnosis and characterization of diseases** and have **potential use in the treatment and cure of cancers.** This group of substances has come to be known as **tumor markers.**

Cancer problem

- A **cancer** is a relatively autonomous growth of tissue.
- A **carcinogen** is an agent that causes cancer.
- **Carcinogen may be:**
 - Physical e.g. radiation.
 - Chemical e.g. polycyclic hydrocarbon.
 - Biological e.g. virus.

- Exposure to such an agent may causes cancer either by:
- **Producing direct genotoxic effects on deoxyribonucleic acid (DNA) e.g.by radiation.**
- **Increasing cell proliferation e.g. By hormone.**
- Or both e.g. (through the use of tobacco).

- *The proliferation of normal cells is thought to be regulated by:*
 - Growth- promoting *oncogenes*.
 - Counterbalanced by growth constraining *tumor suppressor genes*.
- *The development of cancer appears to involve:*
 - The activation or the altered expression of oncogenes.
 - The loss or inactivation of a tumor suppressor gene, or both.

CANCER DEATH (Male)

- Lung and bronchus 31%
- Prostate 11%
- Colon & rectum 10%
- Pancreas 5%

CANCER DEATH (Female)

- Lungs 25%
- Breast 15%
- Colon & rectum 11%
- Pancreas 6%

Tumor markers

- A tumor marker is a substance present in or produced by a tumor or by the tumor's host in response to the tumor's presence.
- Can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurement in the blood or secretions.

- Such a substance can be found in cells, tissues, or body fluids.
- Tumors may secrete a wide range of substances into blood including hormones, enzymes and tumor antigens, which are collectively referred to as **tumor markers.**

Tumor markers cont.

- Tumor markers are substances that can be found in the body when cancer is present.
- They are most often found in the blood or urine, but they can also be found in tumors and other tissue.
- They can be products of the cancer cells themselves, or made by the body in response to cancer or other conditions.
- Most tumor markers are proteins.

- There are many different tumor markers. Some are seen only in a single type of cancer, while others can be found in many types of cancer
- The marker is usually found by combining the blood or urine with man-made antibodies that react with the tumor marker protein
- Most tumor markers can be made by normal cells as well as by cancer cells.

- These substances are normally present in small amounts in the blood or other tissues. Cancer cells can sometimes make these substances. When the amount of these substances rises above normal, cancer might be present in the body. Examples of biomarkers include CA 125 (ovarian cancer), CA 15-3 and 27-29 (breast cancer), CEA (ovarian, lung, breast, pancreas, and gastrointestinal tract cancers), and PSA (prostate cancer).

How are tumor markers used?

1. Tumor markers can be used in a number of ways, including:
2. **Screening** and early detection of cancer
3. **Diagnosing** cancer
4. Determining the outlook (**prognosis**) for certain cancers
5. Determining how well treatment is working
6. Detecting recurrent cancer

N.B:Monitoring treatment and detecting recurrence of disease.(These are the most useful roles for tumor markers).

Clinical Application of Tumor Markers

The potential uses of tumor markers are:

- Screening in general population.
- Differential diagnosis in symptomatic patients.
- Clinical staging of cancer.
- Estimating tumor volume.
- Prognostic indicator for disease progression.
- Evaluating the success of treatment.
- Detecting the recurrence of cancer.
- Monitoring responses to therapy.
- Radioimmunolocalization of tumor masses.
- Determining direction for immunotherapy.

- Tumor markers can be measured **qualitatively or quantitatively** by:
 1. Chemical methods.
 2. Immunological methods.
 3. Molecular biological methods to determine the presence of a cancer.

- Tumors are graded according to their degree of differentiation as :
 - Well differentiated.
 - Poorly differentiated.
 - Anaplastic (without form).
- Tumor markers are the biochemical or immunological counterparts of the differentiation State of the tumor.

Commonly requested tumor markers

- Certain tumor markers may be useful once treatment is complete and there is no sign of cancer in the body.

These include:

- ✓ Prostate specific antigen (PSA) for prostate cancer
- ✓ Human chorionic gonadotropin (HCG) for gestational trophoblastic tumors and some germ cell cancers
- ✓ Alpha fetoprotein (AFP) for certain germ cell cancers and liver cancer
- ✓ CA 125 for epithelial ovarian cancer
- ✓ Carcinoembryonic antigen (CEA) for colon and

Drawbacks of tumor Markers

- Almost everyone has a small amount of these markers in their blood, so it is very hard to spot early cancers by using these tests.
- The levels of these markers tend to get higher than normal only when there is a large amount of cancer present.
- Some people with cancer never have higher levels of these markers.
- Even when levels of these markers are high, it doesn't always mean that cancer is present. For example, the level of the tumor marker CA 125 can be high in women with gynecologic conditions other than ovarian cancer.

Characteristics of Ideal Tumor Markers

1. Specificity for cancer: the substance should be produced only by the tumor.
2. Sensitivity for cancer: a very small tumor growth will produce measurable amounts of marker.
3. The amount of marker produced: will correlate well with the tumor load.
4. The assay for the marker: must be inexpensive, easy to perform, and sensitive.
5. The half- life of the marker: must be short enough, so that when production drops, the level falls off rapidly.

Classification of Tumor Markers

- **Tumor markers are categorized into the following groups:**
 1. Enzymes and isoenzymes.
 2. Hormones, neurotransmitters and their metabolites.
 3. Receptors(estrogen, progesterone, androgen, and corticosteroid).
 4. Serum proteins examples of (immunoglobulins, glycoproteins, carcinoembryonic proteins or oncofetal antigens)
 5. Other markers (sialic acid conjugates, polyamines, and amino acids).
 6. Genetic markers(oncogenes and suppressor gene)

Tumor Antigens

- Include markers defined by *both monoclonal antibodies and polyclonal antisera*, often the so called **oncofetal antigens**.
- The oncofetal substances, present in embryo or fetus, diminish to low levels in the adult but reappear in the tumor.

Tumour markers	Examples
Oncofetal antigens	CEA, AFP
Hormones	Calcitonin, BHCG
Glycoproteins	Ca-125, PSA
Tumour-associated antigens	
Viral antigens	Polyoma, SV 40
MHC-related antigens	H-2k antigen
Enzymes	PAP, NSE, PLAP
Oncogene products	c-myc, c-erbB2
Cytogenetic markers	Ph' chromosome
Tumour-associated markers	
Proteins	Immunoglobulins, beta-2 microglobulin
Enzymes	Lactate dehydrogenase, alkaline phosphatase, pteridines, pterines
Acute-phase proteins	C-reactive protein, ferritin
Inflammatory markers	ESR, viscosity

Marker	Associated non-malignant conditions
AFP	Viral hepatitis, liver injury, inflammatory bowel disease, pregnancy
BHCG	Testicular failure, marijuana smokers, pregnancy
CEA	Smokers, inflammatory bowel disease, hepatitis, cirrhosis, pancreatitis, gastritis
CA 125	Peritoneal irritation, endometriosis, pelvic inflammatory disease, hepatitis, pregnancy
PAP/PSA	Prostatitis, benign prostatic hyperplasia

Enzymes

- *Acid Phosphatase.*
- *Alkaline Phosphatase.*
- *Creatine Kinase.*
- *Lactate Dehydrogenase.*
- *5'-Nucleotidase & Gamma Glutamyltransferase.*
- *Terminal Deoxynucleotidyl Transferase.*
- *Miscellaneous enzymes.*

- Enzymes may have been the first markers used in screening for cancer.
- Each of these enzymes may be elevated in one or more forms of cancer.
- Other enzymes are more specific for cancer these includes: **The collagenase, cathepsin D**, the proteases secreted by malignant cells to break down surrounding tissue being invaded by the tumor.

Acid phosphatase (ACP):

- Acid phosphatase levels increased in patients with :
 1. prostatic adenocarcinoma.
 2. Benign prostatic hyperplasia.
 3. Elevation level of serum prostatic acid phosphatase seen in:
 - **malignant conditions:** such as osteogenic sarcoma, multiple myeloma, and bone metastases of other cancers.
 - **Benign conditions:** such as osteoporosis and hyper-parathyroidism.

Alkaline phosphatase (ALP):

- Elevation, of ALP correlates well with osteoblastic activity and can be used to monitor therapy and look for recurrence in-patients with osteosarcoma.
- ALP is used to differentiate bone and liver malignancy.

Creatine kinase (CK):

- The *BB isoenzyme*, commonly known as the brain fraction, is associated with many malignant diseases.
- Elevations of creatine kinase-BB (CK-BB) may be shown in malignancy in the lung, prostate, breast, ovary, kidney, bladder and brain.

Lactate dehydrogenase (LD):

- Lactate dehydrogenase (LD) is nonspecific marker.
- There is no constant isoenzyme pattern associated with malignancy, but a nonspecific elevation of fraction 2, 3 and 4 is common and called the malignant pattern.
- Benign or malignant tumors shows an increased level of LD.
- Elevations of LD are seen in tumors of the colon, breast, lung, liver and in leukemia and lymphomas.

5'-Nucleotidase and gamma glutamyltransferase (5'-NT and GGT):

- 5'-NT and GGT are both more sensitive markers for liver cancer than ALP.
- They may both be elevated in cirrhosis and GGT, is elevated in a large percentage of pancreatic cancers.

Terminal deoxynucleotidyl transferase (TDT) :

- It is a marker (antigen) found on immature lymphoid cells.
- It can enzymatically synthesize DNA without a template.
- It is used to predict prognosis and responsiveness to drugs as well as to help classify the leukemia.

Miscellaneous enzymes:

- Amylase, lipase, trypsin, ribonuclease are enzymes associated with the pancreas.
- They may be elevated in pancreatic tumors but are frequently elevated in pancreatitis and other diseases of the pancreas.
- **Ribnuclease** may also be elevated in cancers of the breast, colon, stomach, liver and lung.

Enzymes cont.

Collagenase and cathepsin D

- Are part of a large class of compound known as proteases.
- Synthesized and secreted by malignant cells.
- Responsible for degrading the extracellular matrix and thus permitting their invasion and metastasis.
- Collagenase is measured in bone malignancies and cathepsin D is often quantitated in breast cancer patients.

Histaminase or Diamine oxidase:

- Use as marker in case of medullary thyroid cancer to confirm a high level of calcitonin which is normally found in this disease.

Muramidase:

- Muramidase or lysozyme is sometimes used in the monitoring of monocytic and myelomonocytic leukemias.
- It has been reported elevated in some forms of colon cancer.

II-Hormones

➤ The production of hormones in cancer involves two separate routes:

1. *First*, excess production of a hormone by the endocrine tissue that normally produces it.

2. *Second*, produced at distant site by a nonendocrine tissue that normally does not produce the hormone. This latter condition is called ***ectopic syndrome***.

For example :

- The production of *adrenocorticotropic hormone (ACTH)* by the pituitary gland and by the small cell of the lung exemplifies these two routes.

- **N.B:** Hormones may be secreted by tumors of the endocrine glands normally responsible for hormone production (*eutopic production*) or by tumors of other organs that normally do not produce the hormone (*ectopic production*).

- ❖ A benign as well as malignant tumor secretes excessive amounts of hormone.
- ❖ A tumor may secrete multiple hormones, some of which may be synergistic and some antagonistic to each other.
- ❖ A tumor may secrete intact hormones, hormone precursors, fragments, and subunits of hormones.
- ❖ If a non endocrine tumor is found to secrete **ectopic hormone**, that hormone may be used in monitoring the patient during treatment.

APUDoma

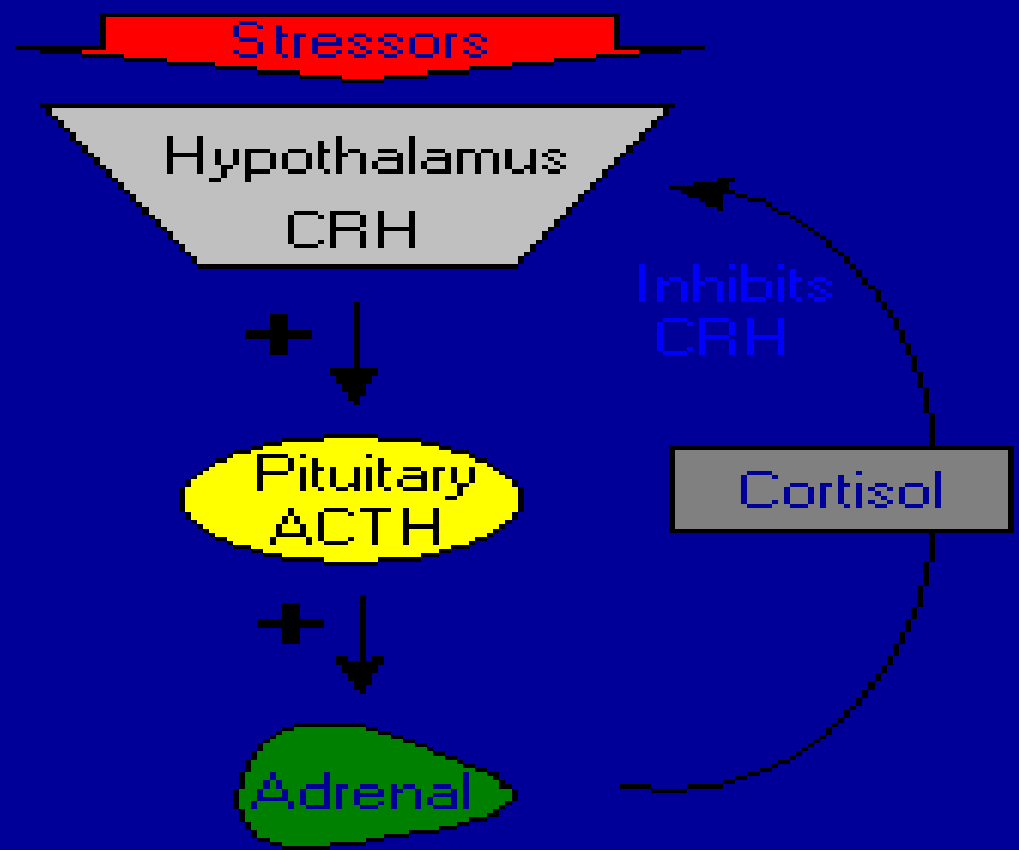
- APUDoma is a group of embryological related tumors of endocrine organs.
- The acronym (APUD) refers to **amine precursor uptake and decarboxylase**.
- APUD cells have properties of both neural and endocrine tissue.
- These tissues synthesize a number of polypeptide hormones such as: ACTH, calcitonin, gastrin, glucagon, insulin, melanosite- stimulating hormone, secretin and vasoactive intestinal polypeptide.

Hormones

- Adrenocorticotrophic Hormone.
 - Calcitonin.
 - Human-Chorionic Gonadotropin.
 - Catecholamines and Their Metabolites.
 - Serotonin and 5-Hydroxyindoleacetic Acid.

Adrenocorticotrophic hormone:

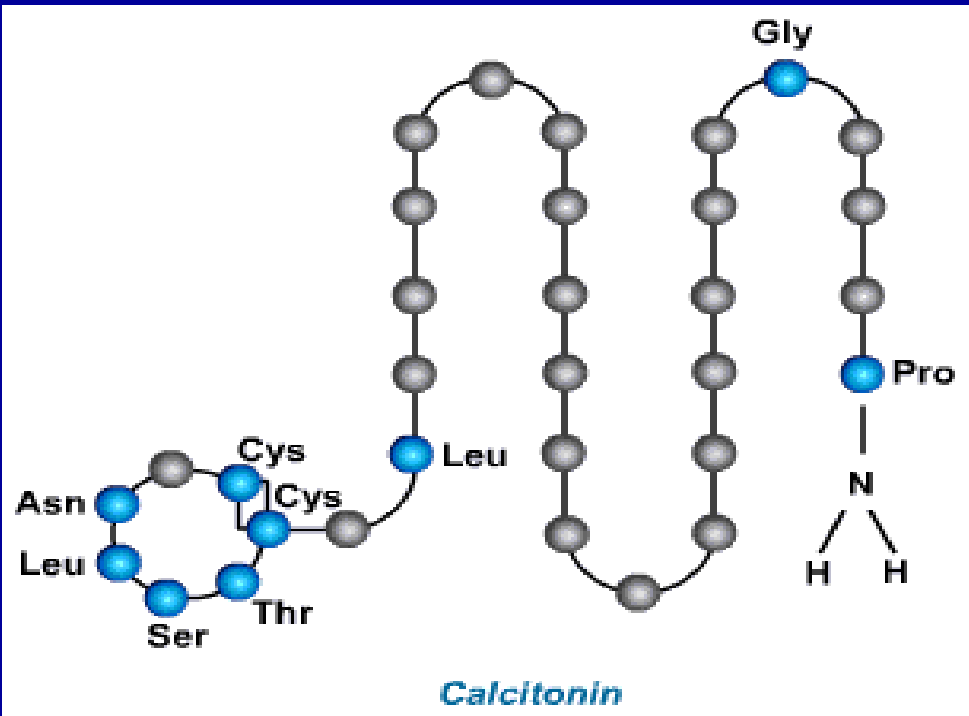
- ACTH is a polypeptide hormone with 39 amino acid and molecular weight of 4500.
- It produced by corticotropic cells of the anterior pituitary gland.
- Elevated serum levels of ACTH the result of **pituitary or ectopic production.**
- A high level of ACTH (>200 ng / L) is of **ectopic origin.**
- Failure of the **dexamethasone suppression test** is also indicative of ectopic production.
- About $\frac{1}{2}$ of the ectopic production of ACTH is due to the **small-cell carcinoma of the lung.**

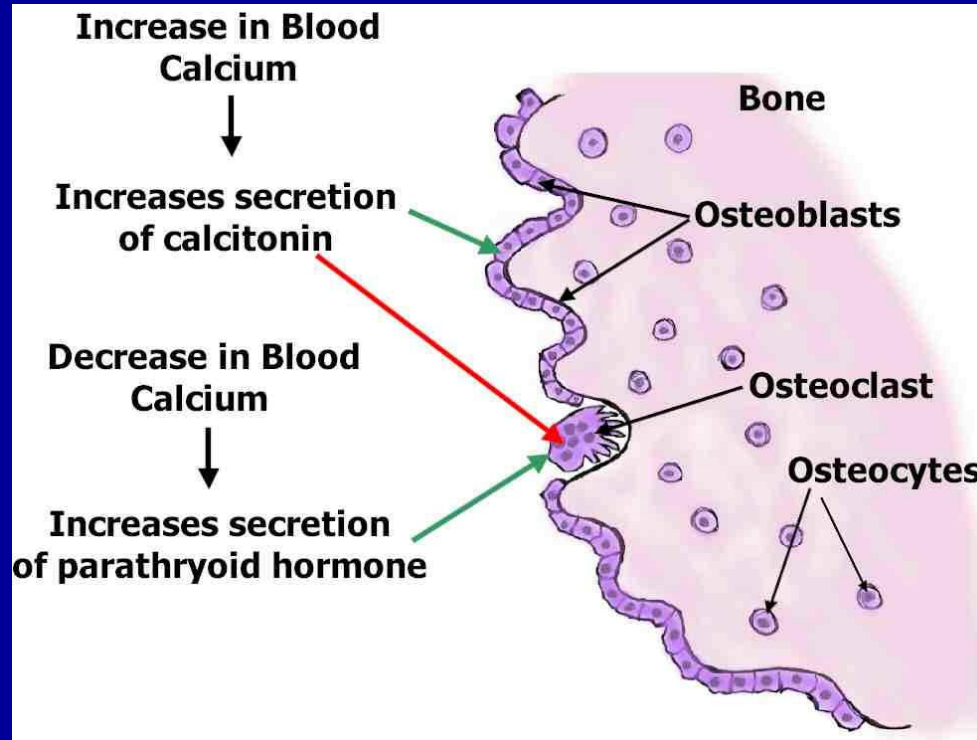


- Other conditions that elevate ACTH levels: Pancreatic, breast, gastric and colon cancer.
- *Benign conditions such as:*
- Chronic obstructive pulmonary disease.
- Mental depression.
- Obesity, hypertension, diabetes mellitus, and stress.

Calcitonin:

- Calcitonin (CT) is a polypeptide. It is formed from 32 Amino acids. Its Molecular weight of 3400.
- It is produced by the **C- cells of the thyroid**. Normally, CT is secreted in response to an increase in serum calcium level.
- It inhibits the release of calcium from bone and thus lowers the serum calcium level.
- The level in healthy individuals is less than $0.1\mu\text{g} / \text{L}$.

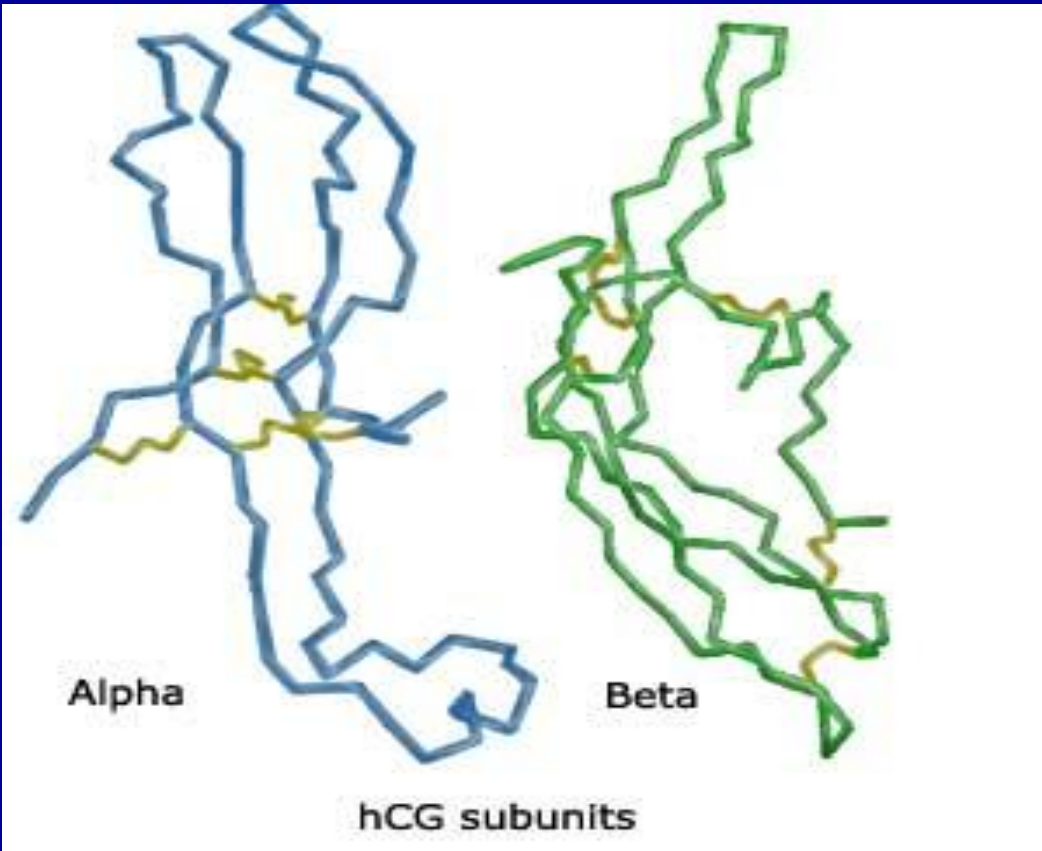




- Elevated level in medullary carcinoma of the thyroid.
- In some patients with cancer of the lung, breast, renal, liver, and carcinoid.
- Other non-malignant conditions such as: pulmonary disease, pancreatitis, hyperparathyroidism, pernicious anemia, paget's disease of bone and pregnancy.
- **N.B.: Calcitonin is most useful in the detection of familial medullary carcinoma of the thyroid, an autosomal dominant disorder.**

Human-chorionic gonadotropin (hCG):

- Human-chorionic gonadotropin (hCG) is a glycoprotein. Secreted by the syncytiotrophoblastic cells of the normal placenta.
- hCG consists of two dissimilar α - and β -subunits. The α - subunit is common to several other hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH).
- The β - subunit is unique to hCG, and the 28 to 30 amino acids comprising the carboxyl terminal are antigenically distinct. hCG has a molecular weight of 45000.



Physiological properties:

- Elevated hCG levels are seen in pregnancy, trophoblastic diseases, germ cell tumors.
- The highest level of hCG (> 1 million *IU/L*) in **trophoblastic tumors**.
- hCG also elevated in some germ cell tumors mainly **non-seminomatous testicular carcinoma**.

- The production of subunits of hCG is under separate genetic control.
- In early pregnancy the free β -subunits is produced together with intact (a whole molecule) of hCG.
- In late pregnancy the free α -subunit is predominates.
- Most cancer patients produce both free β -subunits and intact molecules.

Clinical applications:

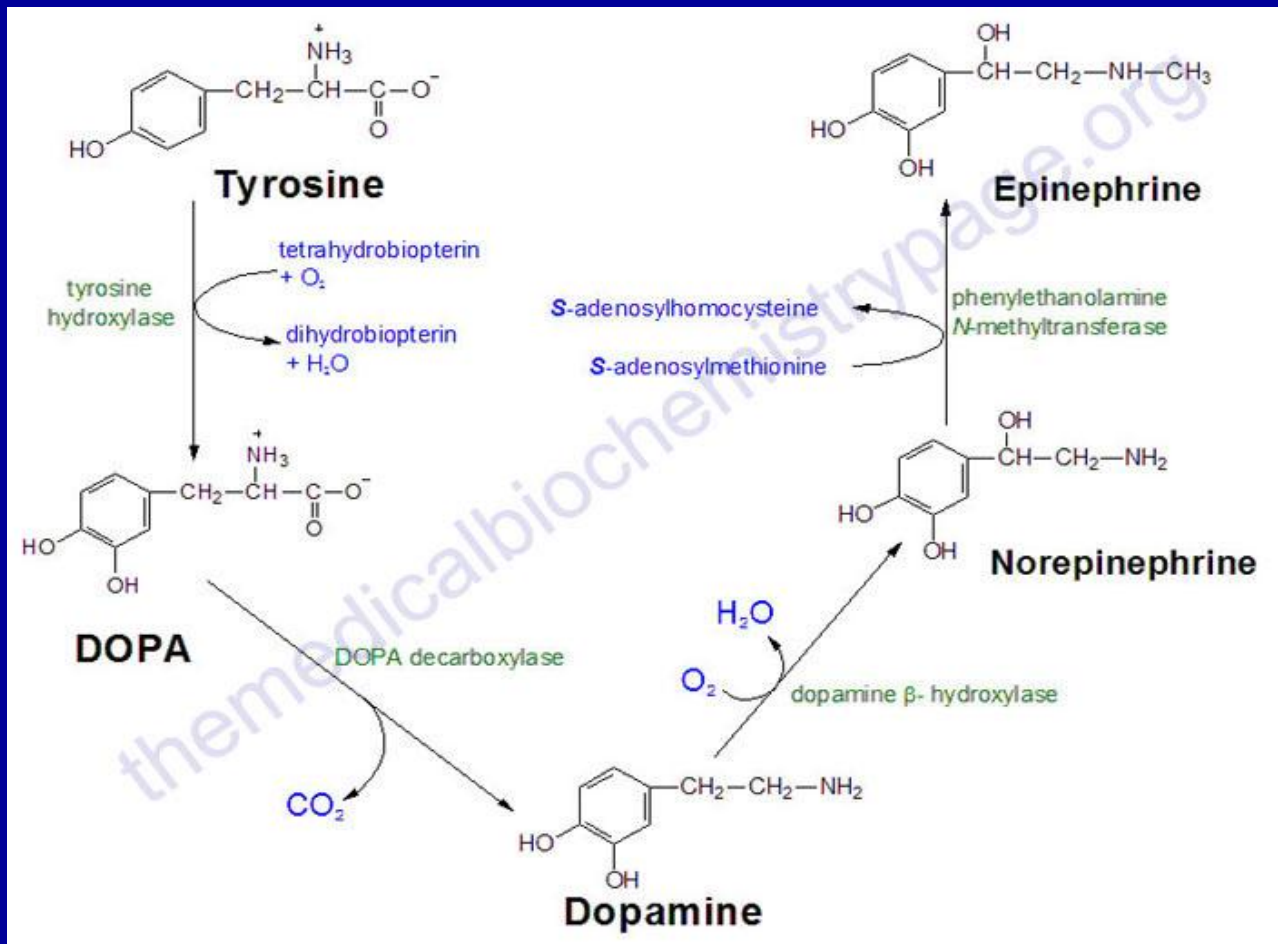
- hCG is elevated in all patients with trophoblastic tumors.
- 70% of these with non seminomatous testicular tumors.
- Less frequently in those with seminoma.
- Lower % of elevation in carcinoma of the breast, GIT, lung, melanoma, and ovarian cancer as well as in benign conditions such as cirrhosis, duodenal ulcer, and inflammatory bowel disease.

- **hCG** is used in conjunction with **alpha-fetoprotein (AFP)** in the classification of germ cell tumors according to their degree of differentiation.
- **hCG** is produced by **syncytial trophoblastic cells**, whereas **AFP** is produced by **the more differentiated embryonic cells**.
- Both **AFP** and **hCG** are measured, and the pattern of elevation or normal value determines which cell types are present.
- Germ cell tumors account for approximately 95% of testicular and 15% - 20% of ovarian tumors.

- hCG is most useful in the monitoring of the treatment and the progression of trophoblastic disease.
- hCG levels correlate with tumor volume. A patient with an initial hCG level of greater than 400,000 *IU / L* is considered at high risk for treatment failure.
- After surgical removal of the tumor, hCG level is expected to decline.
- During chemotherapy, weekly hCG measurement is recommended.
- Slowly decreasing or persistent levels of hCG may indicate the presence of residual disease.

Catecholamines and their metabolites:

- Catecholamines, *epinephrine*, *nor-epinephrine* and *dopamine* are normally produced and stored in the brain and renal medulla, and sympathetic neurons.
- It released in the circulation after sympathetic nerve stimulant , transported by the blood to their target cells, bind to **adrenergic receptors** initiating metabolic and blood pressure change.



➤ Catecholamines are metabolized rapidly after their release into blood. Catecholamine and their metabolites are excreted in to the urine. *The metabolites of catecholamines include:*

- Metanephrine.
- Normetanephrine.
- 3- methoxytyramine.
- Vanilmandelic acid (VMA).
- Homovanilic acid (HVA).

Clinical applications:

➤ Two tumors are associated with production of high levels of catecholamines.

1. Pheochromocytomas in the adult.

2. Neuroblastomas in infants and children.

Pheochromocytomas:

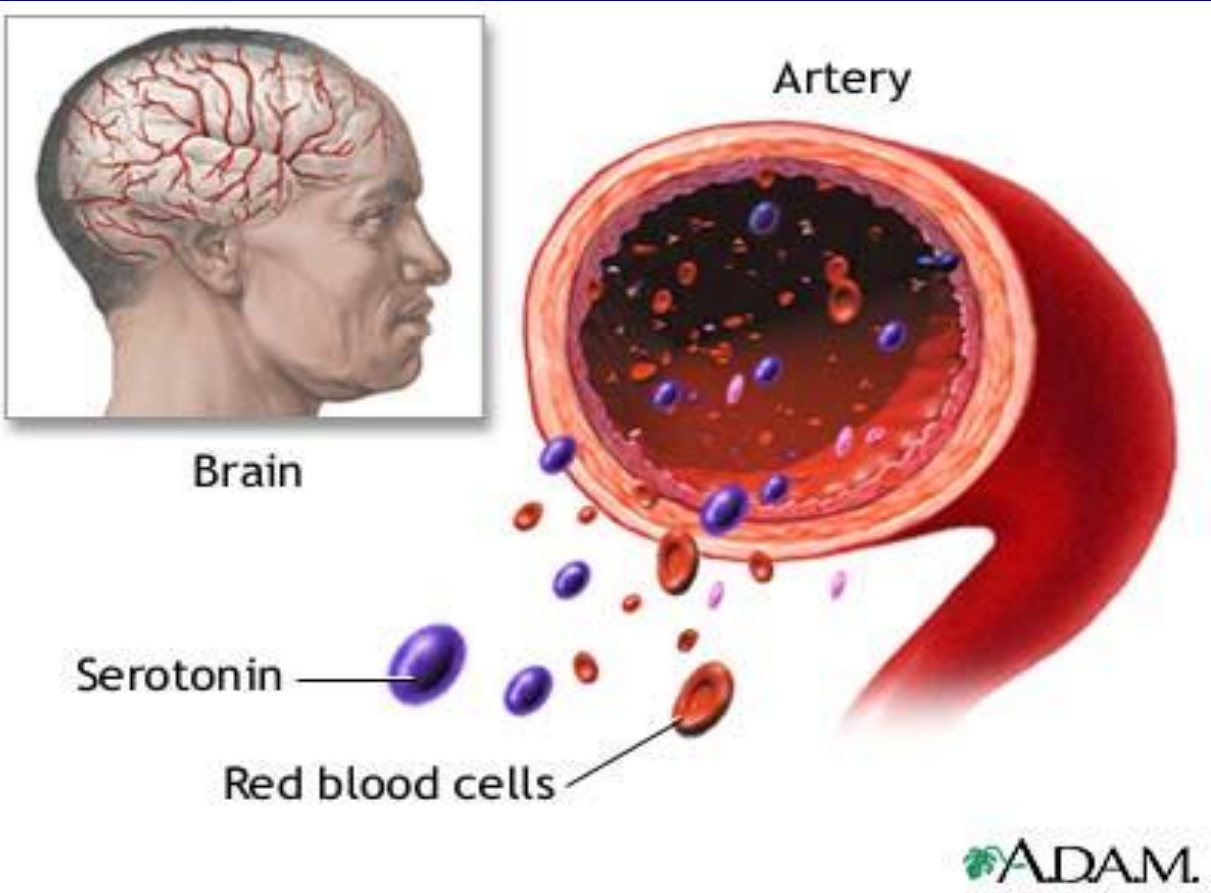
- Pheochromocytomas are tumors of the chromaffin cells.
- It found in the adrenals and sometimes found along the aorta, in thoracic paravertebral ganglia, and along the wall of the urinary bladder.
- It secrete large amounts of catecholamines.
- predominately epinephrine and nor-epinephrine release of the catecholamines is intermittent or sustained and causes hypertension.

Neuroblastomas:

- Neuroblastomas are a common tumor of childhood. It develops in the neural crest tissues in the adrenals, paravertebral tissue or to another place.
- The tumor growth is rapid, with metastasis occurring before diagnosis is made in many cases.
- In infants there are spontaneous tumor regression and there are also cases involving the evolution of the tumor, to a benign ganglioneuroma. The prognosis after a child has reached the age of 1 year is poor. Neuroblastomas secrete norepinephrine.
- **N.B:** Slightly increased levels of catecholamines and their metabolites are usually associated with stress or heavy exercise rather than with a malignant tumor

Serotonin and 5-Hydroxyindoleacetic acid:

➤ Serotonin (5-hydroxytryptamine) is produced in the enterochromaffin cells of the gastrointestinal tract and in the brain and metabolized to 5-hydroxyindoleacetic acid (5-HIAA) in the lungs. Serotonin is a powerful vasoconstrictor that is released during clotting.



Clinical applications:

- Tumors of the enterochromaffin cells called **carcinoid tumors or argentaffinomas**, release increased amounts of serotonin.
- Most of these tumors are primary to the GIT but may also found in the breast, thymus, liver, gall bladder, lung and ovary.

- They grow slowly and may also secrete **histamine, kallikrein, and ACTH.**
- Symptoms of carcinoid tumors *include:*
flushed skin, diarrhea, nousea, asthma, dermatitis, and cyanosis.
- The symptoms depend on the location of the tumor; the associated disease state is called *carcinoid syndrome.*

Hormones cont.

- Antidiuretic hormone.
- Gastrin.
- Glucagon.
- Insulin.
- Prolactin.
- Estrogens and Androgens.
- Thyroid-stimulating hormone.
- Human placental lactogen.
- Growth hormone.
- Parathyroid hormone.
- Erythropoietin.
- Renin and Aldosterone.

Receptors

- Estrogen and Progesterone Receptor.
- Epidermal Growth Factor Receptor.
- Laminin Receptor.

- The study of cell receptors as tumor markers is new, especially when compared with the use of hormones, and enzymes.
- Cell receptors are **protein structure** located on external cell membrane and within the cell.
- It binds with a specific Ligand such as hormone or neurotransmitter. The **ligand-receptor complex** initiates a biologic response.
- There are **defects in receptor production or function** that are inherited, *caused by malignant transformation*, or due to an autoimmune disorder (antibody directed against receptor).
- Because and malignancy causes changes in receptor function and quantity, receptors can be used as a tumor markers.

Receptors used as tumor markers

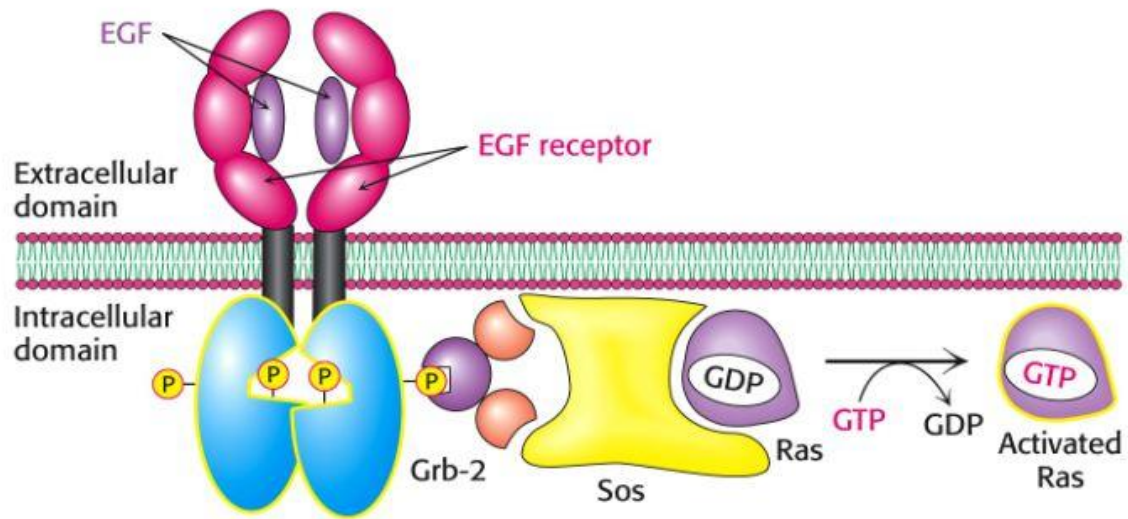
<i>Receptor</i>	<i>Site/tumor or action</i>
Estrogen, progesterone	Breast
Laminin	Measures metastatic potential
Epidermal growth factor	Breast
Interleukin-2	Leukemia

Estrogen and progesterone:

- **Estrogen and progesterone receptors are assayed clinically to determine which breast cancer patients may respond to endocrine therapy.**
- **If tumor growth is stimulated by estrogen, an antiestrogen such as **tamoxifen** may be used to limit the growth of the tumor.**
- **Cell receptor studies are done on a tissue sample obtained from tumor biopsy or excision.**
- ***There are two basic methods of cell receptor quantitation:-***
 1. The ligand-binding assay.
 2. Immunoassay.

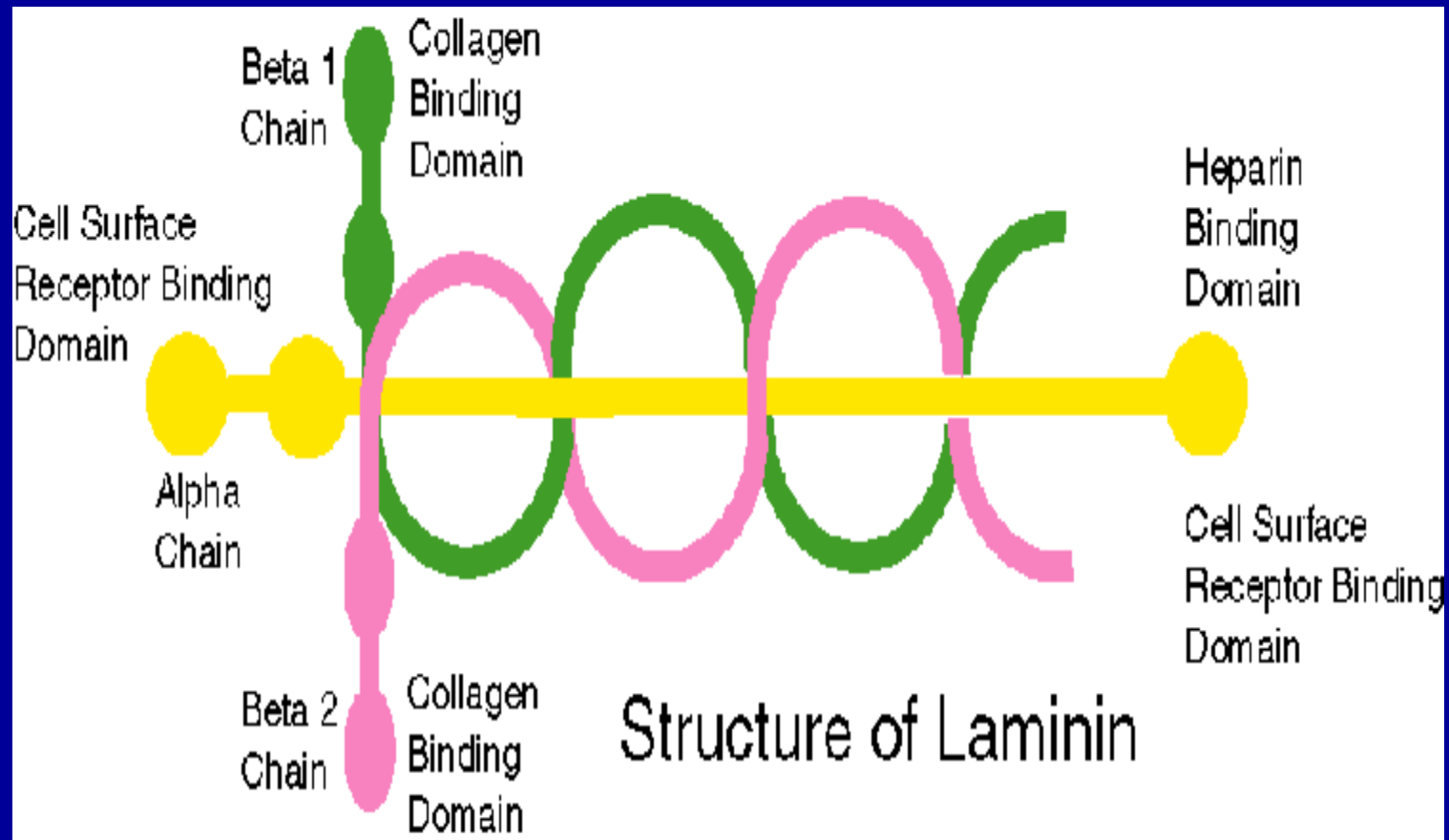
Epidermal growth factor receptor:

- Epidermal is a **glycoprotein** known to bind epidermal growth factor and transforming growth factor alpha.
- The *absence of this receptor* correlate well with a *good response to tamoxifen*.
- **High levels of the receptor** seem to **indicate a poor prognosis** in terms of relapse and patient survival.



Laminin receptor:

- It is a major constituent of basement membrane and binds other important constituents, among them, *collagen, heparan sulfate, proteo-glycan, and entactin.*
- It is another potential marker for **breast cancer.**
- Laminin receptors **allow malignant cells to attach to basement membranes, which are then dissolved, and the cells are destroyed as cancer invades other tissue.**
- Malignant cells have more unoccupied laminin receptors than do normal cells.



Serum Proteins

- Oncofetal Antigens.
- α - Fetoprotein.
- Carcinoembryonic Antigen.
- Tissue Polypeptide antigen.
- Squamous Cell Carcinoma Antigen.
- Prostate-specific-Antigen.
- P-Glycoprotein.
- Sialic Acid.
- Ferritin.
- Beta-2-Microglobulin.
- Hydroxy Proline.
- Immunoglobulins.
- Miscellaneous Proteins.

- **Monoclonal immunoglobulin** has been used as marker for **multiple myeloma** for over 100 year.
- Since monoclonal antibody technology has been developed, and **many previously unknown proteins** use as **cancer antigens**, those tumor markers defined by *antibody*.

Oncofetal Antigens:

- Oncofetal antigens are proteins produced **during fetal life.**
- These proteins are present in **high concentration in the sera of fetuses** and decrease to low levels or **disappear after birth.**
- In cancer patients, these **proteins reappear.**
- The production of these proteins demonstrates that certain genes are reactivated as the result of the malignant transformation of cells.

α -Fetoprotein (AFP):

- AFP is a glycoprotein with a molecular weight of 70,000.
- It consists of a single polypeptide chain and is 4 % carbohydrate.
- It is one of the major proteins **in the fetal circulation.**
- AFP, so named because it **migrates electrophoretically between alpha-1 and albumin**, is the most abundant protein present during fetal development.
- Its function is thought to be similar to that of albumin. AFP is sometimes called **fetal albumin.**

- AFP found in very high levels in the **embryo and fetus.**
- The level gradually drops until the age of about **one year**, when AFP is at normal adult levels (0 to 15 ng / ml).
- α - Fetoprotein (AFP) is a marker for **hepatocellular** and **germ cell(nonseminoma) carcinoma.**
- AFP is associated with various germ cell tumors and **hepatoma.**

Clinical application:

- AFP is a good marker for **primary hepatoma** because it is elevated in approximately 80% of the cases.
- AFP is also elevated in:- *Hepatitis, cirrhosis, several other liver disease.*
- The level of AFP in these cases may help differentiate *benign from malignant* conditions
- It is used as a marker for neural tube defects, and it shows potential, as a screening tool for *Down's syndrome.*

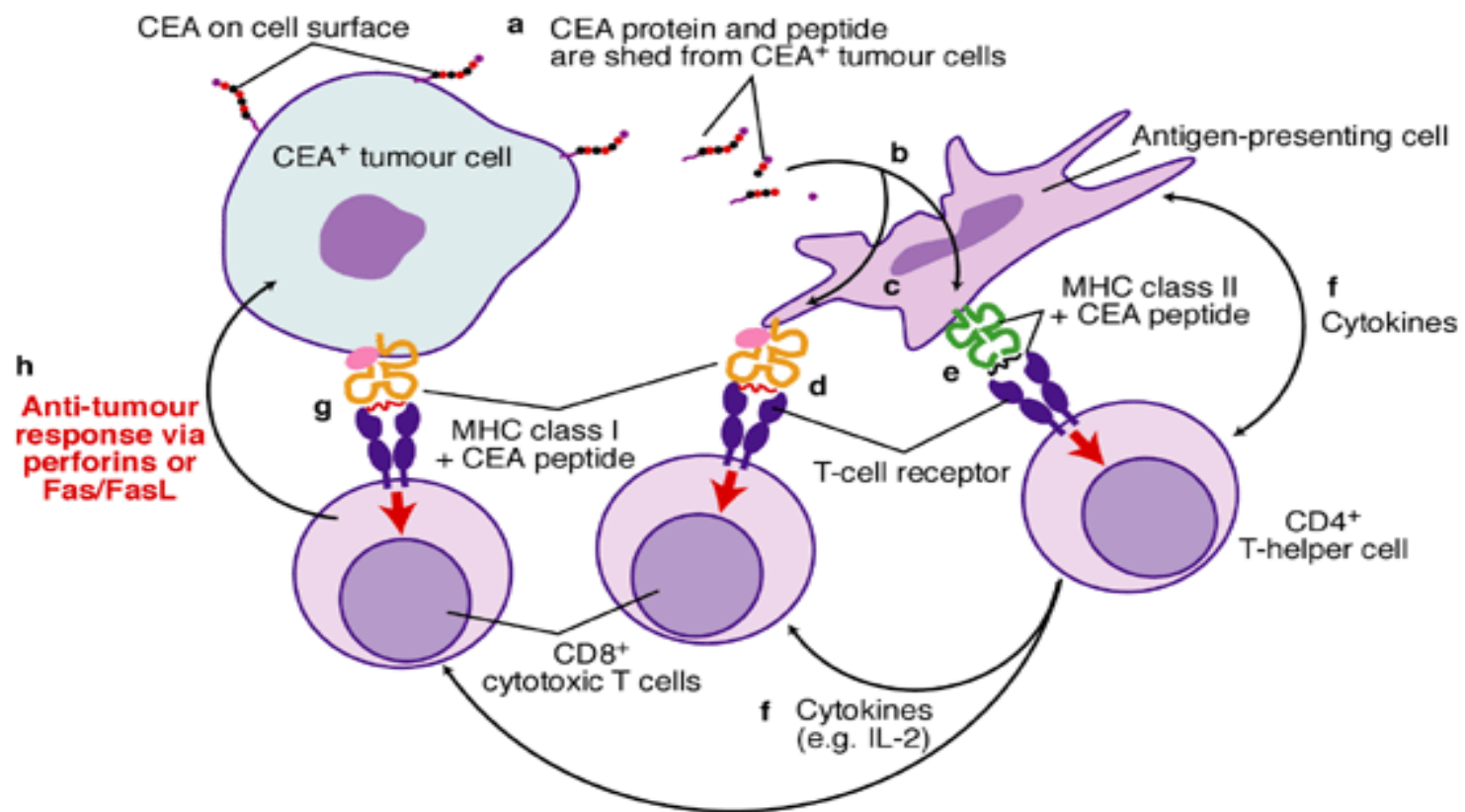
- In *healthy adult* the serum level of AFP is less than **10 $\mu\text{g} / \text{L}$** .
- *During pregnancy*, maternal AFP levels increase from 14 wk. of gestation to a peak of **500 $\mu\text{g} / \text{L}$** during the third trimester.
- The *fetal AFP* reaches a peak of **2 g / L at 14 wk.** and then declines to about **70 mg / L at term.**
- AFP levels **greater than 1000 $\mu\text{g} / \text{L}$** is **indicative of cancer.**
- AFP level is a good indicator for mentoring therapy and the change in clinical status of a patient.

Carcinoembryonic antigen (CEA):

- CEA is a marker for **colorectal, gastrointestinal, lung, and breast carcinoma.**
- It is of the **older oncofetal proteins** in use.
- CEA was discovered by *Gold and Freeman in 1965*, and was originally thought to be specific for colon cancer.

➤ **Biochemistry:**

- CEA is a large family of related **cell-surface glycoproteins**.
- CEA is a glycoprotein with a m. w. of 150 to 300 kd and contains 45 to 55 % carbohydrates.
- It is a single polypeptide chain **consisting of 641 A. A.** with lysine in the N- terminal.
- The CEA family consists of about **10 genes** located on **chromosome 19**.
- Up to **36 different glycoproteins** identified in the CEA family.



Schematic diagram showing how carcinoembryonic antigen (CEA) induces anti-tumour responses mediated by CD4⁺ and CD8⁺ T cells

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Clinical application:

- **In healthy population, the upper limit of CEA is about 3 $\mu\text{g} / \text{L}$ for nonsmokers and 5 $\mu\text{g} / \text{L}$ for smokers.**
- **CEA level is elevated in some patients having benign conditions such as:-**
 - ✓ Cirrhosis 45 % .
 - ✓ Pulmonary emphysema 30 % .
 - ✓ Rectal polyps 2 % .
 - ✓ Benign breast disease 15% .
 - ✓ Ulcerative colitis 15%

➤ **CEA is elevated in a variety of cancers such as:**

✓ Colorectal 70% .

✓ Pancreatic 55% .

✓ Lung 45% .

✓ Gastric 50% .

✓ Breast 40% .

✓ Ovarian 25% .

✓ Uterine 40%

- CEA is also *useful in monitoring breast, lung, gastric, and pancreatic carcinoma.*
- Additionally, CEA is elevated in *alcoholism, inflammation of the bowel, and cystic fibrosis and in heavy cigarette smokers.*
- CEA measured in body fluids other than serum (*ascetic fluid, fluid from cyst, urine, lavage from any cavity*) may also aid in diagnosis.

Tissue polypeptide antigen (TPA):

- Tissue polypeptide antigen is an **oncofetal protein** related to cytokeratins. TPA could be identified by antibodies that react with cytokeratins 8, 18 and 19.
- It is synthesized during mitosis and therefore is a useful marker of **cellular proliferation.**

- TPA is not a specific tumor marker. It is produced by both normal and cancer cells.
- It is elevated in a variety of normal health conditions (pregnancy) and abnormal (autoimmune, infection, and hepatic) conditions.
- It is also elevated in the sera of patients with breast, lung, gastrointestinal, bladder, ovarian, uterine, and prostatic cancers.

- TPA increases throughout gestation and the level returns to normal after 5 days of pregnancy.
- TPA also elevated in inflammatory diseases as well as in cancer, thus, it is not useful for diagnosis.
- TPA may be helpful in the differentiation of cholangiocarcinomas (in which TPA level is elevated) from hepatocellular carcinoma (in which TPA level is not elevate).

Squamous cell carcinoma Antigen (SCC):

- Squamous cell carcinoma antigen is a glycoprotein, previously referred to as “**Tumor-associated antigen 4**” (TA-4).
- Subfractions of SCC antigen have been separated by *isoelectric focusing* into neutral and acidic fractions.
- The molecular weights range from 42,200 to 48,000.
- **Both malignant and nonmalignant squamous cells** contain the neutral fraction, whereas the acidic fraction is found mainly in **malignant cells**.

Clinical application:

- Squamous cell carcinoma antigen is elevated in a variety of SCC including those of the *cervix, lung, skin, head, neck, digestive tract, ovaries, and urogenital tract.*
- SCC antigen is useful in detecting the recurrence of cancer and in the monitoring of treatment and disease progression.

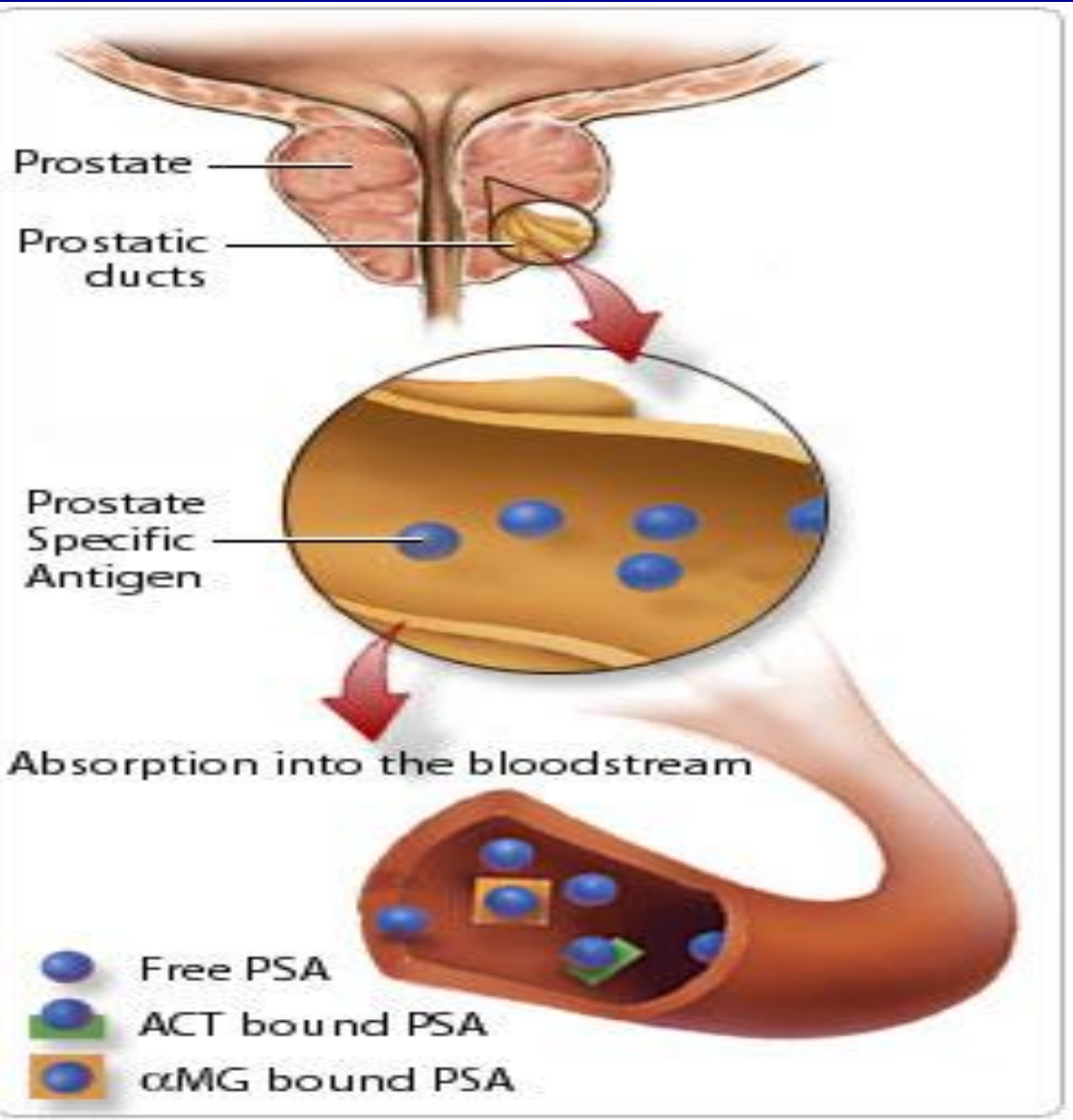
Prostate-specific-Antigen (PSA):

- Prostate-specific-Antigen (PSA) is a **glycoprotein protease** produced in the prostate and secreted into the seminal plasma.
- PSA a single-chain glycoprotein that is 70 % carbohydrate.
- It has **240 amino acid residues** and **four carbohydrate side chains** with linkages at amino acid 45 (asparagine), 69 (serine), 70 (threonine) and 71 (serine).
- The N- terminal amino acid is isoleucine, and the c-terminal residue is proline.
- The molecular weight is 34,000 and it has isoelectric points form 6.8 to 7.2 because of its various isoforms.

➤ The function of PSA is to cause *liquefaction of seminal coagulum.*

Therefore, PSA possesses chymotrypsin-like and trypsin-like activity.

➤ PSA is found in small amounts in normal prostate and is elevated in benign prostate hyperatrophly and adenocarcinoma of the prostate.



Clinical applications:

- Early detection of prostate cancer, PSA testing is not effective in the screening or early detection of prostate cancer because PSA is specific for prostatic tissue but not for prostatic cancer.

Staging of prostate cancer:

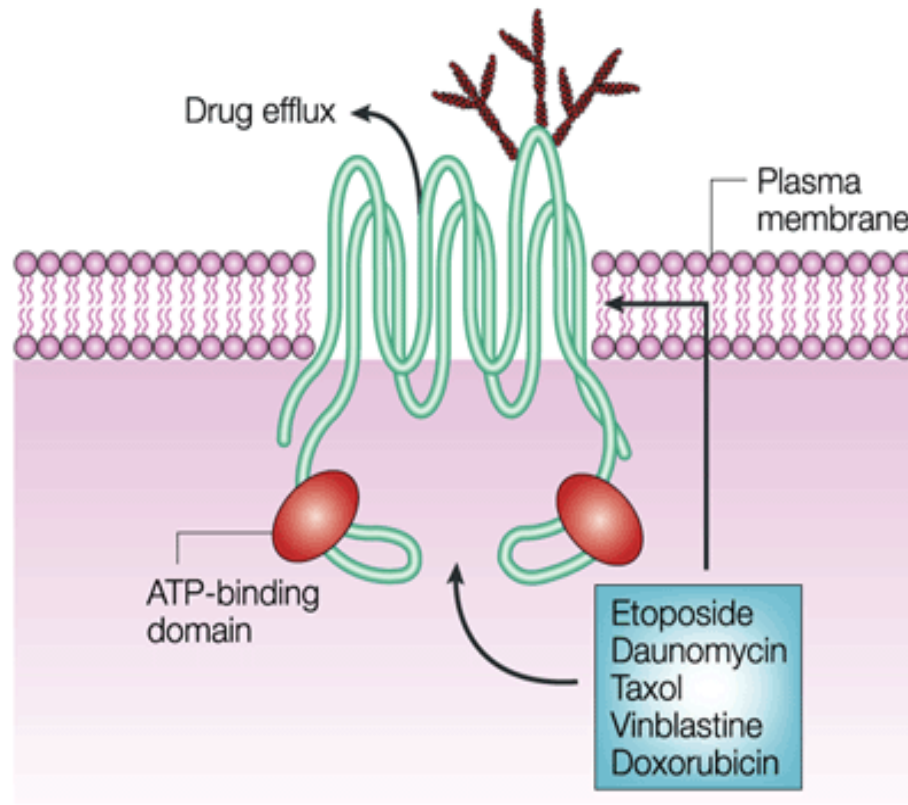
- PSA is found to correlate with clinical stages A to D2 of prostate cancer.
- Higher PSA levels, higher % of patients with elevated PSA concentrations are associated with advanced stages.

Monitoring treatment:

- The greatest clinical use of PSA is in the monitoring of definitive treatment of prostate cancer. This treatment includes:
 - A. Radical prostatectomy.
 - B. Radiation therapy.
 - C. Antiandrogen therapy.
- *Antiandrogen therapy includes:* Bilateral orchiectomy, and treatment with luteinizing hormone-releasing hormone (LHRH) analogue, diethylstilbestrol, and Flutamide.

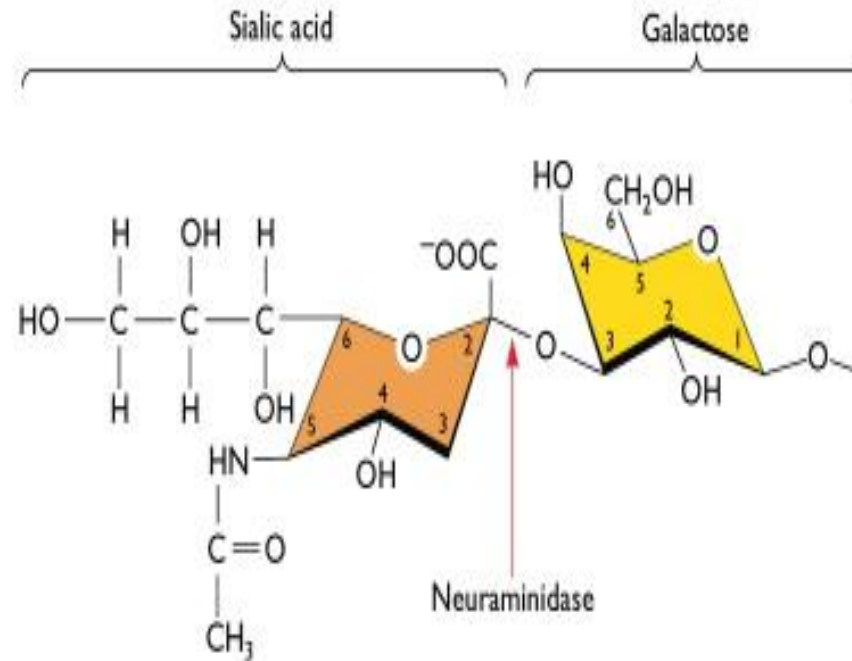
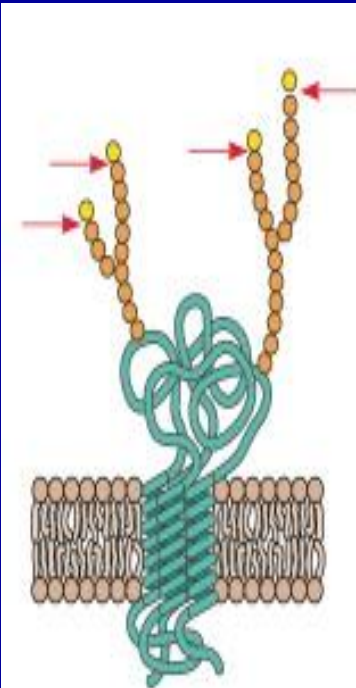
P-Glycoprotein:

- Glycoprotein is found in cell membranes of drug-resistant cells.
- It is normally found in cells of the kidney, liver, adrenals, and GIT. Most tumors that develop in these organs are fairly drug resistant. Cells resistant to one drug, may also show resistance to other unrelated drugs, a phenomenon called **multi drug resistance**.
- It is theorized that-P-glycoprotein is active in transporting the drugs out of the cells. P-glycoprotein measured using a monoclonal antibody, C219. The tumor cells are stained with labeled antibody or tagged and counted using flow cytometry.



Sialic acid:

- Sialic acid is a family of **acylated derivatives of neuraminic acid** usually found on the terminal end of the carbohydrate portion of glycoprotein or glycolipid in cell membranes.
- It is non specific marker for **malignant neoplasia**. The carbohydrate portion may influence cell-to-cell interaction, affecting cohesion, adherency and antigenicity.
- These characteristics change after malignant transformation of a cell. The level of sialic acid may be altered with the change.



Ferritin:

- Ferritin is a serum protein responsible for binding and transporting iron in the serum. It is an indicator of iron status. It is directly proportional to the body iron stores.
- Ferritin is elevated in any disease that causes disturbance in iron metabolism and erythropoiesis.
- It may be elevated in:- **Hepatitis, aplastic anemia, leukemias, myeloma, gastric, colon, pancreatic, lung, and breast cancers, and melanoma.**
- Levels also affected by *secondary complications of cancer* such as **obstruction and anemia.**
- Ferritin released from malignant tumors has a ***more acidic isoelectric point*** than normal ferritin and thus may be differentiated by **isoelectric focusing.**

Beta-2-microglobulin (B2M):

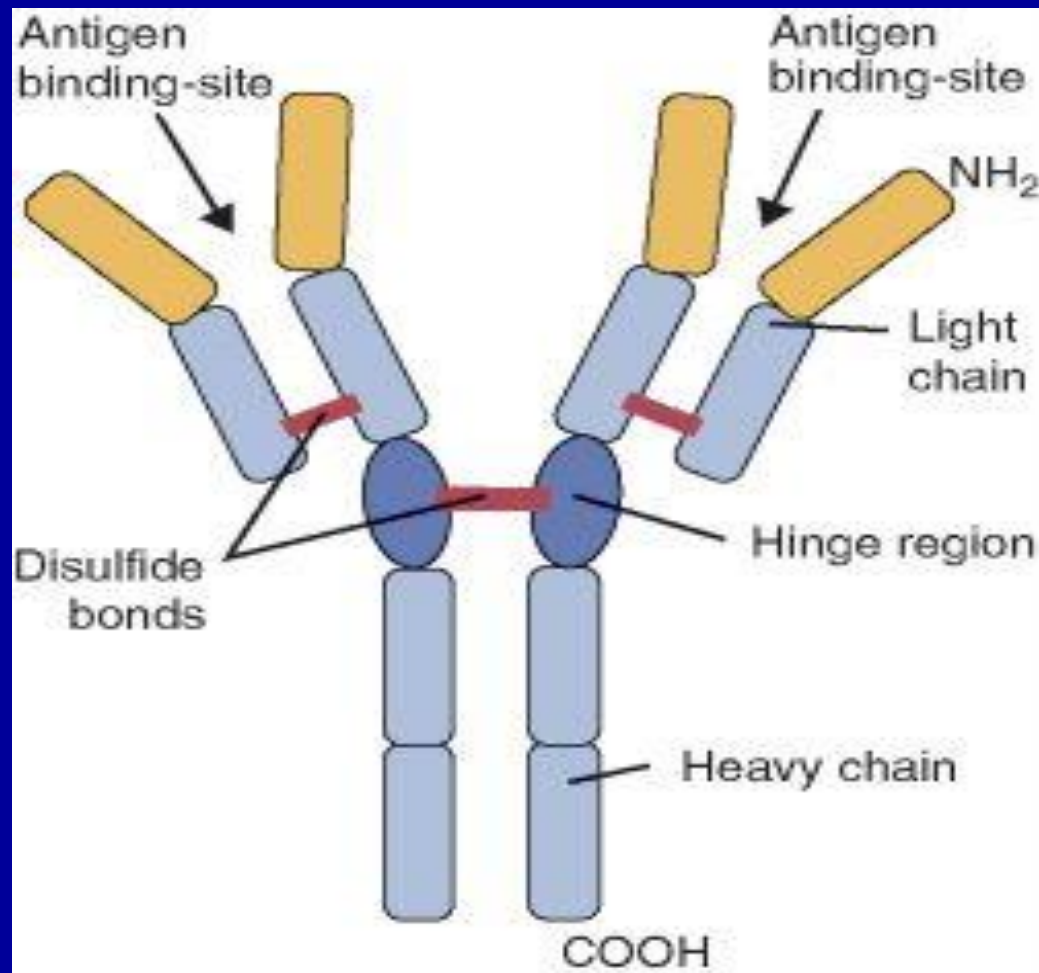
- Beta-2-microglobulin is an antigen found on the surface of all nucleated cells.
- It is a **subunit of human leukocyte antigen (HLA)** and is elevated in **all diseases associated with rapid cell turnover.**
- It is used as a marker for:- **leukemia, lymphoma, and multiple myeloma, and it correlates well with B-lymphocyte activity.**
- It may also be elevated in patients suffering from **human immunodeficiency virus (HIV) infection.**

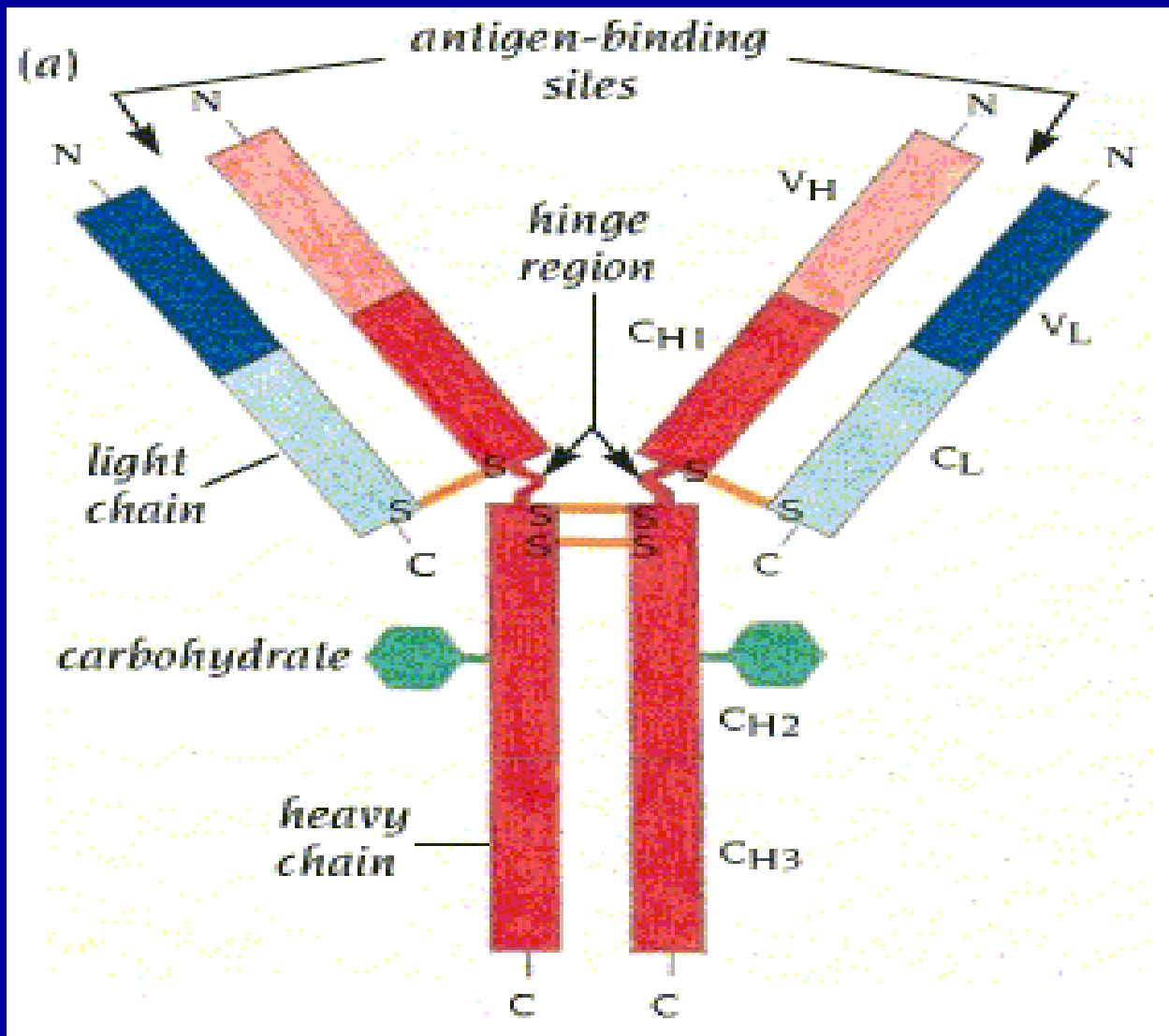
Hydroxy proline:

- Hydroxy proline is an amino acid, that is **elevated in patients with bone metastases.**
- It is measured in urine using HPLC.

Immunoglobulins:

- The immunoglobulins have been used as markers in **multiple myeloma** and in **waldenstrom's macroglobulinemia** for many years.





Miscellaneous proteins:

- Polyamines (putrescine, spermine and spermidine) are stabilizing agents that associate with cell membranes and nucleic acids.
- The polyamines are metabolic products produced by all proliferating cells and acetylated in the liver.
- Since their concentration in urine appears to parallel the rate of proliferation, they have been **used to monitor therapy and recurrence of disease.**
- They are measured in urine by HPLC or GC.
- They may have use as markers in **brain tumors.**

Carbohydrate Markers

1. High Molecular Weight Mucins
2. Mucin Like Carcinoma Associated Antigen
3. Blood Group Antigens

- Carbohydrate-related tumor markers are either:-
 - ✓ Antigens on the tumor cell surface.
 - ✓ Or those that are secreted by the tumor cells.
- It is more specific than naturally secreted markers such as enzymes and hormones.
- ❖ Carbohydrate markers are:-
 - i. High-molecular-weight mucins.
 - ii. Blood group antigens. CA15-3, CA549 and CA27.29 are markers for breast carcinoma.

CA15-3

- CA15-3 is a glycoprotein not specific but sensitive for **breast cancer. It is a marker for breast carcinoma.**
- Elevated CA15-3 levels are also found in **other malignancies, including:-**
 - ✓ Pancreatic 80%
 - ✓ Ovarian 64%.
 - ✓ Lung 71 %.
 - ✓ Heart 69%.
 - ✓ Colorectal 63% .
 - ✓ Liver 28%.
- Also elevated CA15-3 levels in benign disease : e.g.
 - ✓ In benign liver 42%.
 - ✓ In benign breast disease 16 %.

- CA15-3 is most useful in *monitoring therapy* and *disease progression in metastatic breast cancer patients*.
- *CA549, breast cancer mucin (BCM), and mucin-like carcinoma-associated antigen (MCA)* are new breast cancer markers that may show similarity to CA15-3.
- The upper limit of CA15-3 is 25ku /L in healthy subjects.

CA 549:

- CA549 is a **marker for breast carcinoma**. It is an acidic glycoprotein.
- In a population of healthy women, 95% of the population have CA549 values below 11 ku /L.
- Pregnancy and benign breast disease show minimal elevation.
- Patients with benign liver disease show slight elevation.
- CA549 has been shown to be **elevated in a variety of non breast metastatic carcinomas including:-**
 - ✓ Ovarian 20% carcinomas.
 - ✓ Prostate 40% carcinomas.
 - ✓ Lung 33 % carcinomas.

CA 27.29:

- CA 27.29 is a **marker for breast carcinoma.**
- In a healthy population of 500 individuals, the upper limit was 36.4 ku/L.

Mucin like carcinoma-associated antigen (MCP):

- Mucin like carcinoma-associated antigen (MCA) is a **marker for breast carcinoma.**
- It is a glycoprotein with a molecular mass of 350 kd.
- In 100 healthy women the upper reference limit for MCA was found to be 14 ku/L. MCA levels increase throughout pregnancy.
- MCA levels is elevated in 60% of **metastatic breast cancer patients.**

- Elevated levels also found in:
ovarian, cervical, endometrial and prostatic carcinoma.
- Minimum elevation is observed in **benign breast disease.**
- In the *monitoring of metastatic breast cancer patients*, changes in MCA levels parallels those of **CA15-3** levels.

CA 125:

- CA 125 is a good **marker for ovarian carcinoma.**
- CA 125 is a high molecular mass glycoprotein. It contains 24% carbohydrate.
- In a healthy population, the upper limit of CA 125 level is 35 ku /L.
- It has been found to be elevated in non-malignant conditions such as: pregnancy, endometriosis, fibromatosis, pelvic inflammatory disease, pancreatitis, and peritonitis.

- The highest levels are associated with **ovarian cancer**, but CA 125 is elevated in other malignancies.
- CA 125 is elevated in non ovarian carcinoma including: **Endometrial, pancreatic, lung, breast, and colorectal and other gastrointestinal tumors.**

DU-PAN-2:

- **DU-PAN-2 is a marker for pancreatic cancer.**
- **Du-PAN-2 of serum levels are elevated in patients with **pancreatic (54-61%), biliary tract (44-47%), and hepatocellular (44%) carcinomas.****

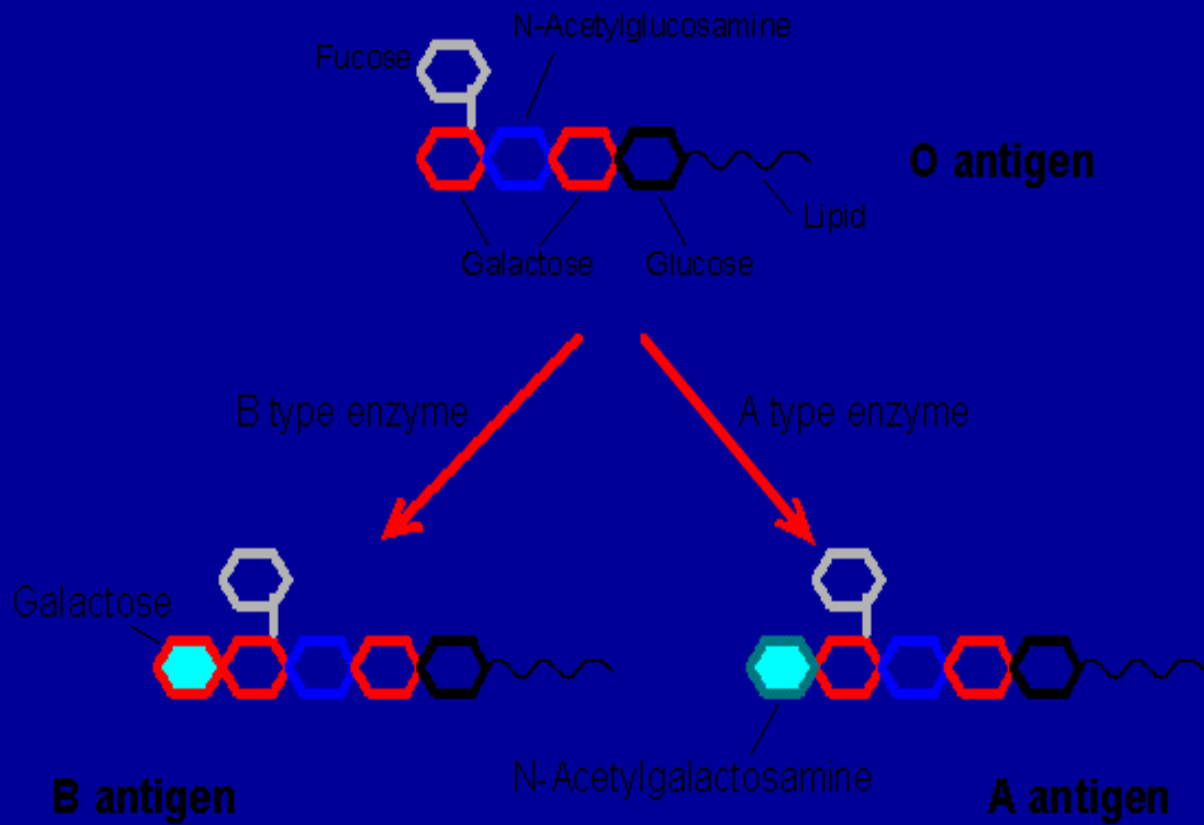
Blood group antigens:

- These include:- CA 19-9 , CA50, CA 72-4 and CA 242.

CA19-9:

- CA19-9 is a mucin like oligosaccharide characterized by antibody first developed from mice immunized to a human colon cancer cell line (SW-1116).
- CA 19-9 is a marker for **both colorectal and pancreatic carcinoma.**
- CA19-9 Is used clinically to monitor therapy and to predict disease recurrence.

- CA19-9 may also be elevated in diseases associated with **biliary obstruction and in cystic fibrosis.**
- CA 195 , CA 50, CA242, pancreatic oncofetal antigen (POA), and Du-Pan-2 are other antibody-defined markers that may exhibit similar specificity and sensitivity for pancreatic carcinoma.



CA 50:

- CA 50 is a marker for pancreatic and colorectal carcinoma. The cut-off values of healthy is 14-20ku / L.
- CA 50 is a monoclonal antibody developed against the human colonic adenocarcinoma cell line Colo 205.
- Elevated level of CA 50 reported in:-
 - ✓ Benign disease of the pancreas (12-46%).
 - ✓ Biliary tract (35-38%).
 - ✓ Liver(22-59%).
 - ✓ In pancreatic cancer, 80-97% of patient.
 - ✓ In colon cancer, elevated levels were reported in Duke's A (19-43%), B (30-59%), C (53-73%) and D (53-73%).

➤ In digestive tract carcinoma, elevated levels were seen in esophageal (41-71%), gastric (41-78%), biliary (58-70%), and hepatocellular (14-78%) cancer.

➤ **Other malignancies** were reported to have lower percentages of elevation, including **breast, lung, renal, prostate, bladder, and ovarian cancer.**

CA72-4:

- CA 72-4 is a marker for carcinomas of the gastrointestinal tract, lung and of the ovary.
- Tissue polypeptide antigen (TPA) is an oncofetal protein similar to CA 72-4 in its nonspecific elevation in neoplastic disease.
- A cut-off of 6ku /L is used in the CA 72-4.
- The following percentages of elevation were observed:-
 - In health 3.5 %.
 - In benign gastrointestinal disease 6.7%.
 - In gastrointestinal carcinoma 40%.
 - In lung cancer 36%.
 - In ovarian cancer 24%.

CA 242:

- CA 242 is a marker for **pancreatic and colorectal cancer.**
- It is a monoclonal antibody developed from a human colorectal upper reference limit is 20 ku/L.

Blood group antigen-related cancer markers

<i>Name</i>	<i>Antibody</i>	<i>Type of cancer</i>
CA19-9	19-9	Pancreatic, GIT, hepatic
CA19-5	19-5	GIT, pancreatic, ovarian
CA 50	C50	Pancreatic, GIT, colon.
CA 72-4	B27.3,cc49	Ovarian, breast, GIT,colon
CA 242	C242	GIT, pancreatic

Mucin tumor markers

<i>Name</i>	<i>Antibody</i>	<i>Type of cancer</i>
CA 125	OC125	Ovarian, endometrial
Episialin: CA15-3	DF3&115D8	Breast, ovarian.
CA549	BC4E 459, BC4NL54	Breast, ovarian.
CA 27-29	B27.29	Breast
MCA	b-12	Breast, ovarian.
Du-PAN-2	DU-PAN-2	Pancreatic, ovarian, GIT, lung

Genetic Markers

- There are two types of genetic tumor markers:
 - Oncogenes.
 - Anti-oncogenes (suppressor genes).

- Cancer is an inheritable characteristic of cell and must be the outcome of genetic changes. Multiple genetic alterations may be necessary for the transformation of a cell from a normal state to a cancerous one and, finally, for metastasis, therefore, the evaluation of chromosomal changes may fill the gap left by the traditional serum biochemical markers in establishing the risk index and the screening for cancer.
- Two classes of genes are implicated in the development of cancer:
 1. **Oncogenes.**
 2. **Anti-oncogenes (Suppressor genes).**

- ***The Oncogenes*** are derived from normal cellular genes (**proto-oncogenes**), which are involved in regulating cellular growth, proliferation, differentiation, and apoptosis (**programmed cell death**).
- The oncogenes are activated by mutational events that cause **increased transcription of growth and proliferation, promoting protein products or products which antagonize (suppress) normal cellular apoptosis.** Mutation include, insertion, deletion, translocation, inversion and point mutations.
- Most human oncogenes are associated with **hematological malignancies** such as **leukemia** but few are associated with **solid tumors**

➤ *The suppressor genes* have been isolated from solid tumors. The oncogenicity of suppressor gene is derived from the loss rather than the activation of the oncogenes. Deletion or monosomy may lead to the loss of tumor suppressor genes.

Oncogene markers

<i>Oncogene</i>	<i>Function</i>	<i>Product</i>	<i>Type of cancer</i>
N-ras- mutation	Signal transduction	Tyrosine kinase	Acute myeloid leukemia, neuroblastoma
C-myc Translocation	Transcription regulation	Binds to DNA	B- & T-cell lymphoma, lung (small-cell)
C-erb-B-2- amplification	Growth factor receptor	Tyrosine kinase	Breast, ovarian, gastrointestinal
C-abl/ber translocation	Signal transduction	Tyrosine kinase	Chronic myelocytic leukemia
N-myc amplification	Transcription regulation	Binds to DNA	Neuroendocrine

Oncogenes:

- Proto-oncogenes are normal cellular genes. Activation of proto-oncogenes is found to be associated with cancer.
- Oncogenes are involved in growth factor signaling pathways.
- Amplification of the oncogene will lead to abnormal cell growth, resulting in malignancy.
- More than 40 proto-oncogenes, only a few shown to be useful tumor markers.

ras Genes:

- The ras genes are closely related genes that code for tyrosine kinase.

C- myc Gene:

- The C- myc gene is the proto-oncogene of avian leukemia virus. It binds to DNA and is involved in transcription regulation.

C-erb B-2 Gene:

- The C-erb B-2 gene is also called HER-2/neu owing to its association with neural tumors (neu), in addition, its gene product, p65, is similar to the epidermal growth factor receptor.

Suppressor genes:

- The study of suppressor genes may provide a clue as to the development of cancer from normal cell status to benign and cancerous statuses and to metastasis.

Suppressor gene markers

<i>Suppressor gene</i>	<i>Chromosome</i>
Dcc (deleted colon carcinoma)	18q21.3
Nf-1 (neurofibromatosis)	17q11.2
RB (retinoblastoma)	13q14
P53	17q
Wt (wilms' tumor)	11 P13
erb-B-2	7p

Other markers

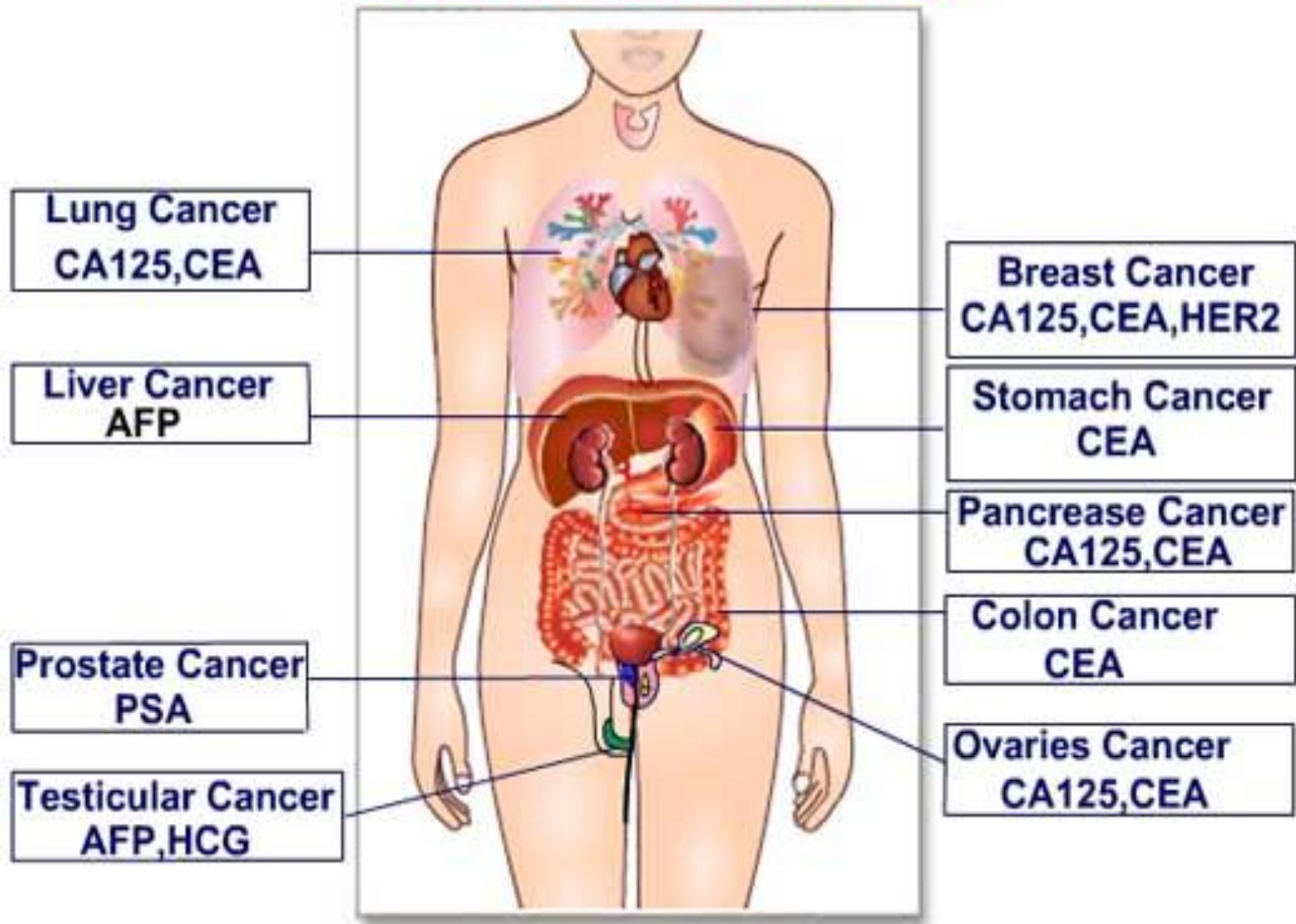
Includes:

- Lipid-Associated Sialic acid.
- Hydroxyproline.
- Polyamines and Acetylated polyamines.
- Blood Cell Surface Antigens.

Clinical Applications

- **Gastrointestinal cancers.**
- **Breast cancer.**
- **Ovarian cancer.**
- **Uterine cancer.**
- **Testicular tumors.**
- **Skin cancer.**
- **Neuroblastomas and pheochromocytomas.**
- **Leukemias and lymphomas.**
- **Miscellaneous tumors.**
- **Bronchogenic carcinoma.**
- **Pancreatic cancer.**
- **Prostate adenocarcinoma.**

Clinical Tumor Markers



Gastrointestinal cancers

- The tumor markers used to monitor patients with colon cancer include: CEA, CA 19-9 and CK-BB.
- In gastric cancer the tumor markers are CEA, CA 72-4 , C19-9 and CK-BB.

Breast cancer

- More tumor marker options are available for use in evaluating breast cancer than for most other cancer. Serum markers include:CEA, CA 15-3, BCM, CA 549, MCA, ferritin, and CK-BB.
- Tissue can be analyzed for estrogen and progesterone receptors, cathepsin D, epidermal growth factor, laminin receptor, ploidy, C-erbB-2 and collagenase. PSA may be used rather than surgery to evaluate the risk of disease recurrence.

Ovarian cancer

- Tumor markers are used to classify tumors, to follow therapy, and to replace surgery for detecting metastasis and recurrence.
- Tumor markers for ovarian cancer include: CA125, OCA, AFP, CEA, HCG, CA72-4, and sialic acid.
- Examination of the ratio of CA125 to CEA may help differentiate ovarian cancer from other abdominal cancer

Uterine cancer

- Tumor marker include :-
SCC for squamous cell carcinoma, TPA, sialic acid, and histaminase.

Testicular tumors

- Tumor markers are very important in this cancer and are used by doctors to follow its course.
- These tumors are classified partially by the presence of abnormal levels of the tumor markers Human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP) .
- LD may also be used as a marker in testicular cancer.

- There are different kinds of testicular cancers, and they differ in the level and kind of marker that is elevated.
- **Seminoma:** About 10% of men with seminoma will have elevated HCG. None will have elevated AFP.
- **Non-seminoma:** More than half of men with early stage disease will have elevated HCG or AFP or both. These markers are elevated in most men with advanced disease. Very high levels of these markers

- HCG is almost always elevated and AFP is never elevated in **choriocarcinoma**, a **subtype of non-seminoma**.
- In contrast AFP, but not HCG, is elevated in another subtype known as **yolk sac tumor or endodermal sinus tumor**.
- Many tumors are made up of a mixture of different types of non-seminoma.

Skin cancer

- Tumor markers are not used extensively with skin cancer, Diagnosis is made by biopsy, and microscopic examination and treatment involve surgical removal or cryotherapy.

Neuroblastomas and pheochromocytomas

- Tumor markers associated with tumors of the brain and central nervous system include:-
Catecholamines and metabolites,
CK-BB, CEA, and the
polyamines, spermine and
spermidine.

Leukemias and lymphomas

- TDT is a marker associated with acute lymphoblastic leukemia.
- B2M is associated with several lymphomas and with multiple myeloma.
- The Philadelphia chromosome is closely associated with chronic myelocytic leukemia and multiple myeloma or plasma cell myeloma is associated with increased amounts of IgG.

Miscellaneous tumors

- Less common are tumors of the bladder, kidney and primary hepatoma.
- The marker of choice for bladder tumor is CEA. And for kidney tumors, erythropoietin, renin, and parathyroid hormone (PTH).
- Primary hepatoma, may follow hepatitis, cirrhoses or viral disease. Markers for primary hepatoma include:- AFP, GGT, LD, and 5-NT.
- Metastases to the liver are very common, and the markers associated with primary hepatoma, may also be elevated in metastatic disease.

Cancer	Marker(s)	Recommended use
Breast	CEA, CA 15-3	M
Carcinoid	5-HIAA	D
Hepatoma	AFP	S, D, P, M
	CEA	M
Gastrointestinal*	CEA	P, M
	CA 19-9	
Ovary	CA 125	P, M
	CASA	P, M
Prostate	PSA	D, P, M
	PAP	P, M
Germ-cell tumours	AFP	D, P, M
	BHCG	D, P, M
	LDH	P, M
	PLAP (seminoma)	P, M
Choriocarcinoma	BHCG	D, P, M
Thyroid	Thyroglobulin	S, M
Neuroblastoma	VMA	D, P, M
	Catecholamines	D, P, M
	NSE	M
Myeloma	Immunoglobulins	D, P

D, diagnosis; P, prognosis; S, screening; M, monitoring course of disease or response to therapy.

* Colorectal, stomach and pancreatic carcinomas.

Other Common cancers and the tumor markers linked to them

- **Bladder cancer** : No tumor markers in urine are recommended for bladder cancer screening.
- Bladder tumor antigen (BTA) and the NMP22 tests can be used along with cystoscopy for diagnosis Normal values may allow cystoscopy to be done less often. These tests do not take the place of urine cytology and cystoscopy.

➤ For advanced bladder cancer, some of the markers used for other cancers such as CEA, CA 125, CA 19-9, and TPA may be elevated and can be used to follow patients during and after treatment.

Gestational trophoblastic disease

- **Trophoblastic tumors** include **molar pregnancies** (a pregnancy that results in a tumor of the placenta) and **choriocarcinoma**.
- Human chorionic gonadotropin (HCG) is elevated in these tumors.
- HCG testing can be used to find these cancers in women who are no longer pregnant but still have an enlarged uterus.
- HCG measurements during treatment for trophoblastic disease are very useful in looking at response to treatment.

Liver Cancer

- Higher AFP levels occur in most patients with liver cancer.
- Screening with AFP has been successful in parts of Asia where liver cancer is common.
- A rising AFP level might be a sign of cancer.
- AFP can be used to follow patients after curative surgery or other treatment.

Lung Cancer

- No tumor markers have proven useful as screening tests for lung cancer.
- tumor markers that may be elevated:
- **carcinoembryonic antigen (CEA)** in non-small cell carcinoma
- **neuron-specific enolase (NSE)** in small cell lung carcinoma.
- Sometimes doctors will follow these markers to evaluate treatment . But because lung cancer is easily seen on chest x-rays tumor markers play a less important role.

Multiple Myeloma

- no tumor markers commonly used to screen for this disease
- tests for immunoglobulins can be used to help detect/make a diagnosis.
- Protein electrophoresis and immunofixation can find these immune system proteins in the blood or urine of most patients with myeloma.
- Pieces of immunoglobulins in the urine, called Bence Jones proteins, are found in some patients

- Detectable levels of a certain immunoglobulin, a monoclonal or M-protein, in the blood.
- A monoclonal spike, or M spike, on a protein electrophoresis is noted and help diagnose the disease,
- bone marrow biopsy may be needed to confirm dx
- helpful in monitoring and response to treatment.
- higher blood levels of beta-2-microglobulin, which can also give information on outlook

Pancreatic CA

- No markers have been found to be helpful in screening
- The CA 19-9 marker is the most useful marker
- Most people with pancreatic cancer have elevated levels of CA 19-9 in their blood. The higher the level, the more likely the disease has spread.
- CA 19-9 levels give information about the outlook for people with pancreatic cancer but cannot be used to diagnose the disease

Gastric carcinoma

- No marker has been developed for this cancer.
- Some other digestive cancer markers may be elevated, such as CEA, CA 72-4, and/or CA 19-9.
- If the levels of these markers are elevated at the time of diagnosis, the levels can be followed while the cancer is being treated.

New in Tumor Marker Research

- **Genomics:** study of patterns of DNA changes (or mutations) that may detect early cancer
- **Proteomics:** looks at the patterns of all the proteins in the blood instead of looking at individual protein levels.

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