Tumor markers, paraprotein

Author: Eva Klapková

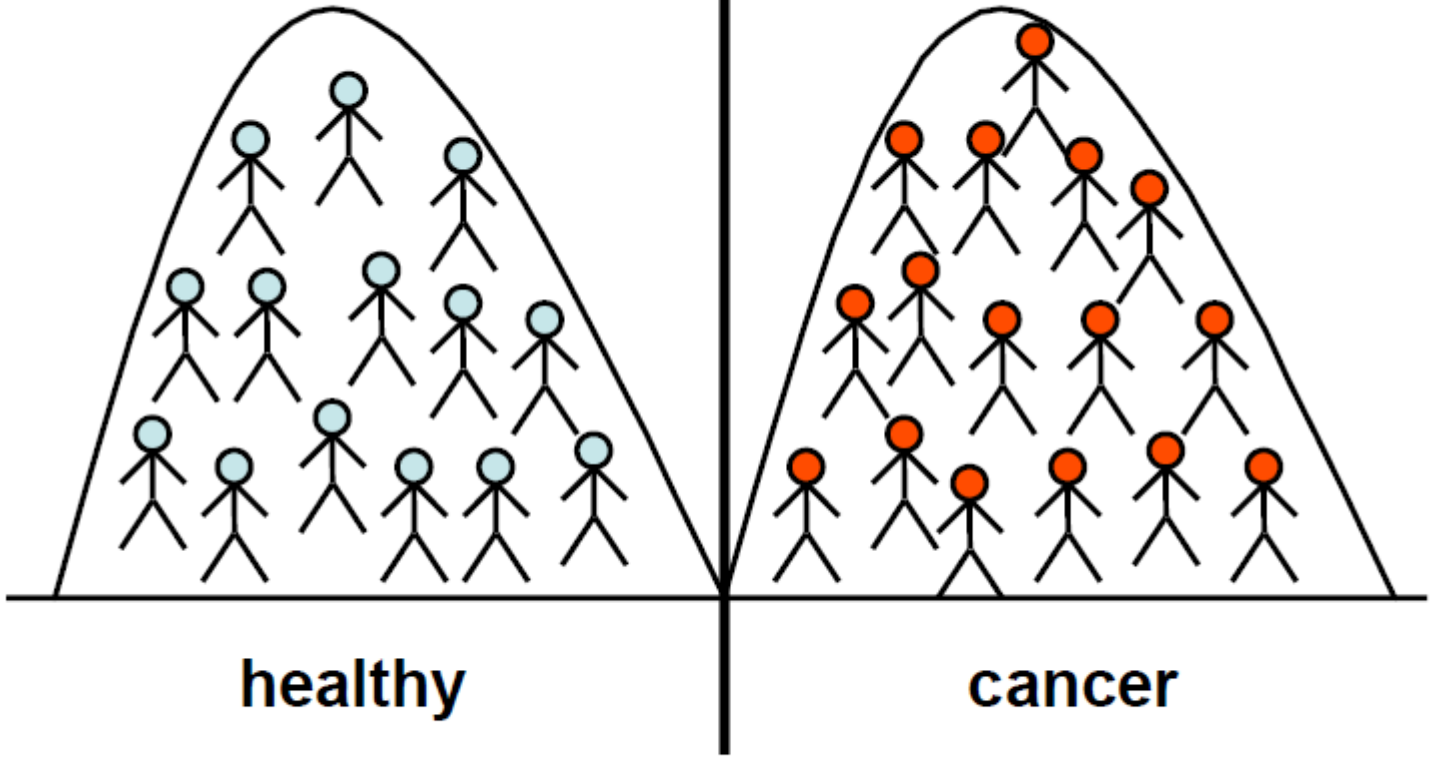
- substances present in the tumor or produce by the tumor or by the host as the response to the presence of the tumor

- predominantly protein substances

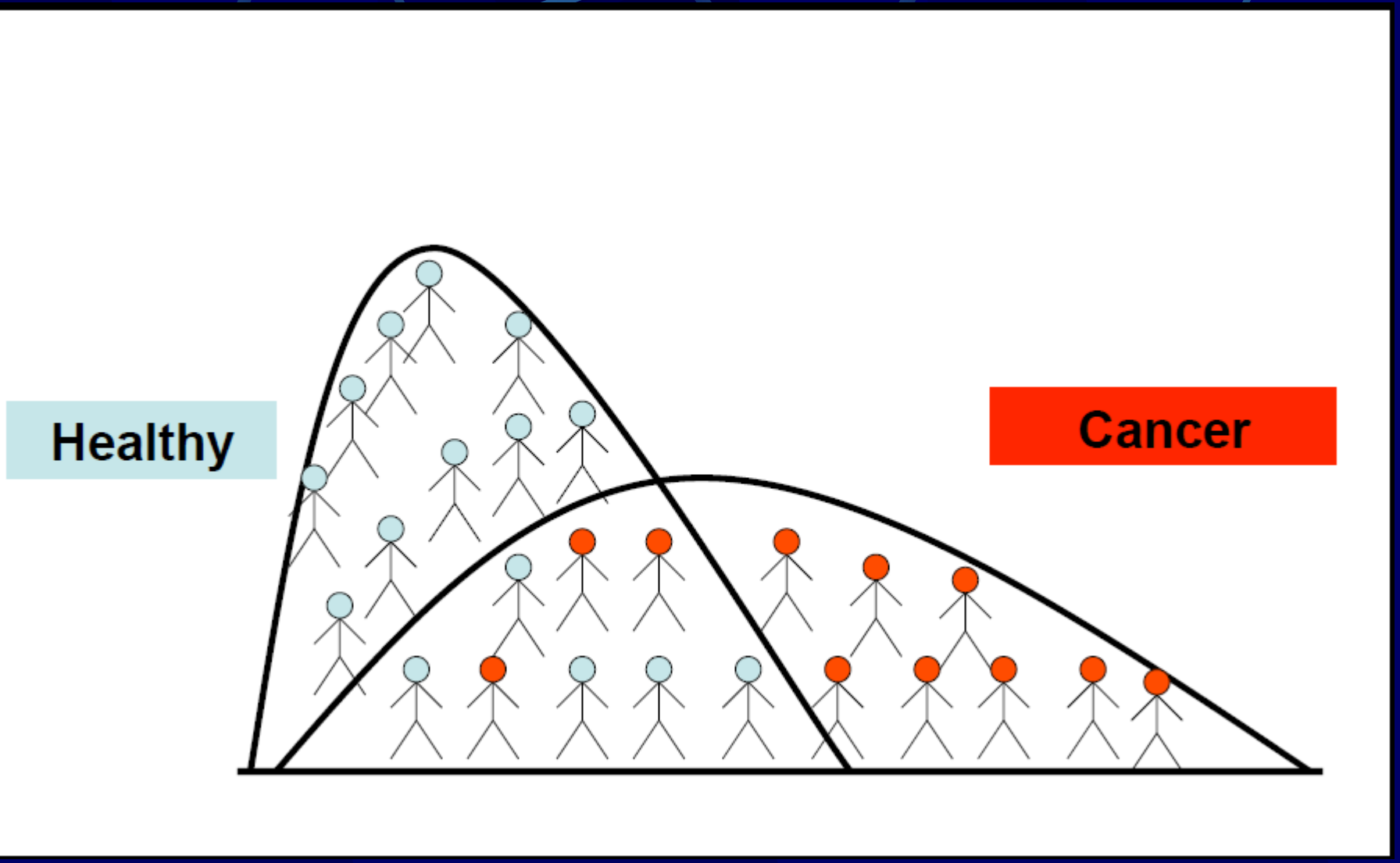
Markers, which are detectable in biological fluids, tissues or cells, by means of which it can be demonstrated:

- **risk of developing**
- **presence**
- **prognosis**
- **metastatic process**

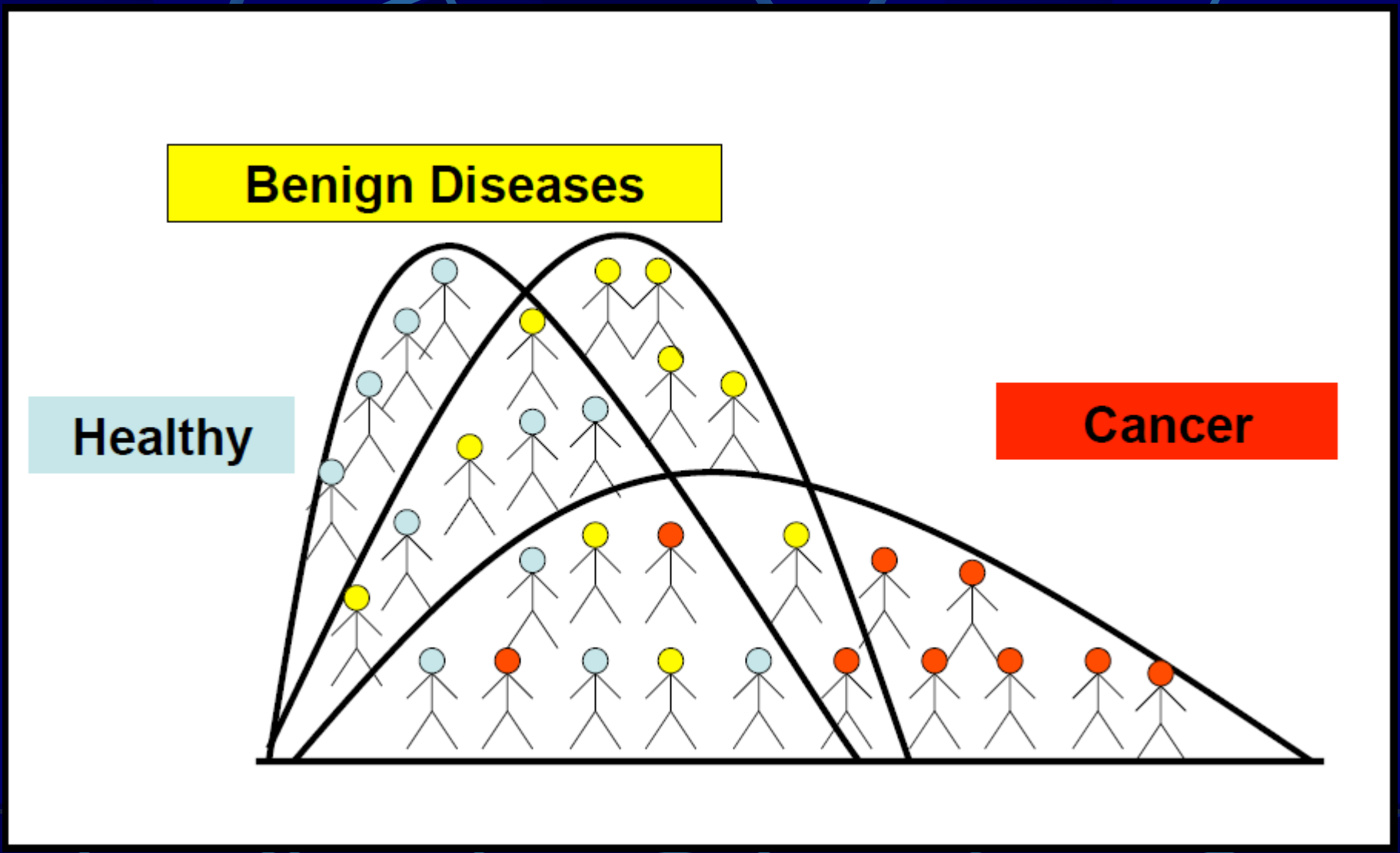
Still far away from our wish

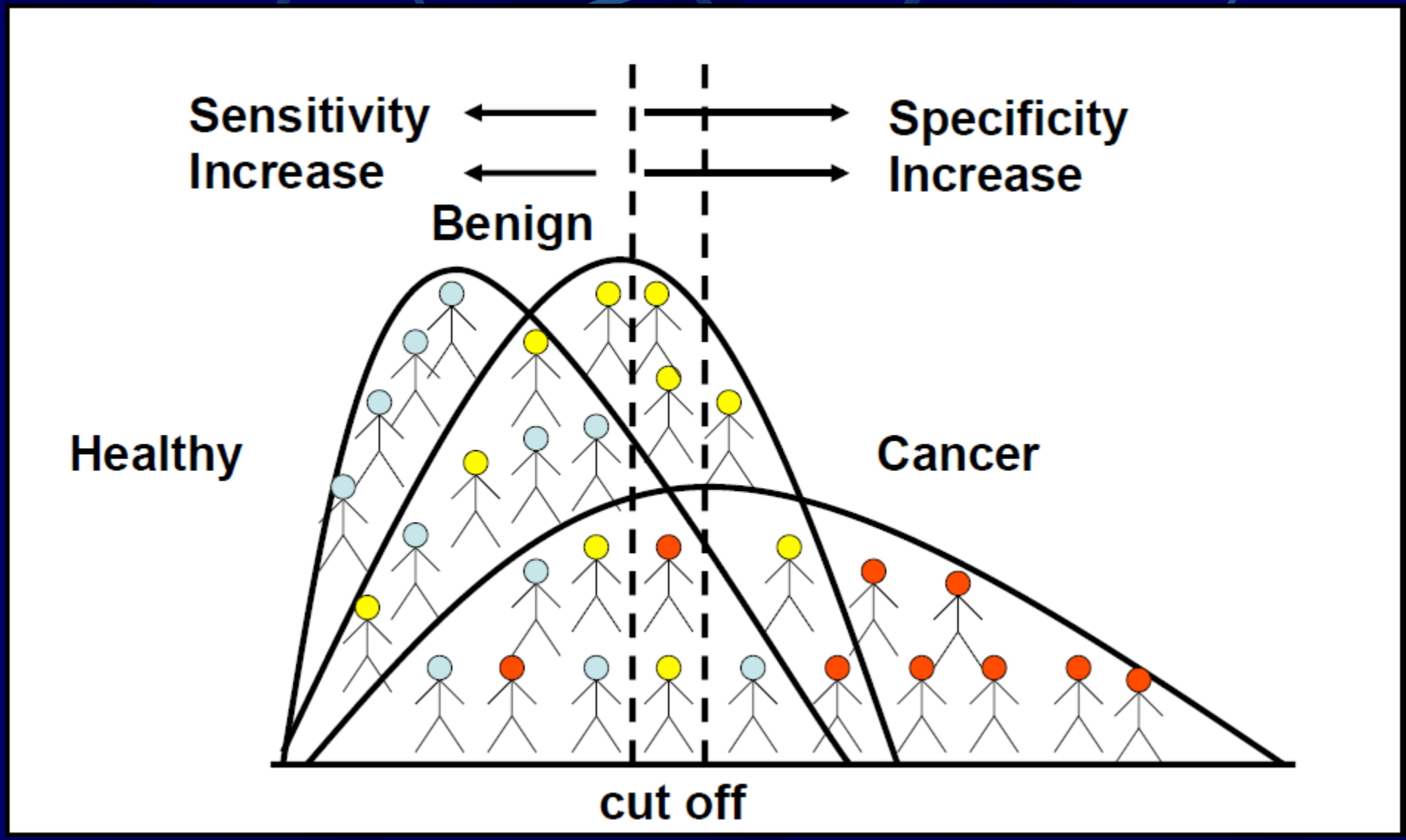


Reality of oncological biomarkers



Reality of oncological biomarkers




Sensitivity
Increase
Specificity
Increase
Benign
Healthy
Cancer
cut off

Production

- by cancer
  (tumor associated antigens)

Antigens

* oncofetal (AFP, CEA ..)
* oncoplacental (hCG, isoenzymy ALP)
* „Carcinoma antigens“ (CA-19-9, CA 15-3..)
* paraproteins

-Hormones (kalcitonin, catecholamins..)

-Enzymes (NSE ..)

-(Receptors)

- by other tissues

Properties of ideal tumor marker:

- should be produce directly by the tumor
- organ-specific
- in biological fluids it should be in high concentrations (highly sensitive)
- concentration of tumor marker should correlate with:
  - tumor size
  - tumor stage
  - high prognostic value
  - effect of tumor therapy

Currently, no such tumor marker is known

Main function of tumor markers

- monitoring stage of the disease
- monitoring the treatment

Classification of tumor markers

- by determination
- by chemical structure
- by function
- by organ-specificity

humoral **– determination in body fluids**

cellular- **determination by immunohistochemical techniques in cancer tissue**

Chemical structure

- glycoproteins
- carbohydrates
- glycolipids
- polypeptides
- immunoglobulins
- polyamines

Function

- oncofetal antigens
- enzymes
- hormones
- receptors
- others

Organ specificity

- **high:** calcitonin – medullary carcinoma of the thyroid
  PSA/PAP – carcinoma prostate
  NSE – small cell lung carcinoma
  hCG – germ cell tumors
  AFP – primary hepatocellular carcinoma, germ cell tumor

- **relatively high:** CA 19-9 – carcinoma pancreas
  CA 125 – epithelial carcinoma of ovary
  CA 15-3 – breast carcinoma

- **relatively low:** CEA, TPA

Organ specificity

- low during examination only one marker
- it can be increased by combination of two markers
- for each malignancy we distinguish me major and complementary tumor marker

Major marker

- marker with high sensitivity and specificity for one type of malignancy
- it is possible to have more major markers for selected malignancy

Complementary marker

- marker of second choice
- determined together with first choice marker
- nonspecific tumor markers have a poor sensitivity, nevertheless their concentrations are sensitive to any alterations in tumor volume

- **in combination with the marker of first choice, better detection of malignancy**
- **the use of multiple markers based on the combination pattern for the selected malignancy will improve sensitivity and specificity of the detection**

Oncofetal antigens

- Substances, which are produced by fetal tissues and also in much lower concentration by adult tissues
- Produce by tumors in higher concentrations
- Quantitation of t. marker concentration can be valuable aid in prognosis and in monitoring of the treatment
- Most tumor markers belong to this group

- př.: CEA, AFP, hCG, CA 15-3, CA 19-9, CA 50, CA 72-4, CA 125

Enzymes

can be devided in to two groups:

1. **enzymes involved in cell division**

   Enzymes are found in plasma at higher levels when the cancer involves the

   important for determination of prognosis and stage of tumor
2. **enzymes that are native to normal tissue, where performed their biological function**

   high organ specificity – determination of tumor localization

- E.g..: 1) TK, 2) NSE, PAP, PSA

Hormones

1. Hormone is produced by associated organ (by endocrine cells) - calcitonin by medulla thyroid carcinoma

   or

2. Ectopic production (hCG small cell lung Ca)

- Check the effectiveness of the treatment

- E.g.: ACTH, ADH, PTH, hCG, calcitonin, prolactin, TG

Others

1. Tissue products, that can not be classified into any groups
2. Nonspecific substances produced as the response to the presence of the tumor

- 1) TPA, TPS, CYFRA 21-1, VMA, 5-HIIA
- 2) ferritin, β_2-microglobulin, imunoglobulines

Other classification

Oncofetal antigens- compounds produce normally for a while in fetal life, after birth is produce especially by cancer tissue

AFP, hCG, CEA

Tissue-and organ specific- compounds, which may be present as intracellular substances in tissues, can be released into the circulation during malignancy process

PSA, NSE, CA, SCC, TG, TPA, TPS,

Nonspecific antigenes, enzymes, hormones

LDH, ACTH, parathormon, ADH

Clinical application

- **screening – most of tumor markers is not suitable (low specificity and sensitivity)**

  - can be useful in high-risk groups

Tum. marker	Risk group	Risk of cancer
AFP	cirrhotic patients, consequence of viral hepatitis	liver carcinoma
TPA	Workers at risk of organic cancers	bladder cercinoma
calcitonin	Familial occurence	medullary carcinoma of the thyroid
paraprotein	benign monoclonal hypergamaglobulinemia	multiple myeloma
PSA	Men > 50 let	prostate carcinom

- **Primary diagnosis and confirmation**
  mostly not suitable for the same reasons as screening (AFP, NSE)
- **staging – reflect tumor burden in the body**
- **prognosis – only some markers are suitable for prognosis - CEA, AFP, hCG, β_2-microglobulin**
- **monitoring – most important function**
  - rising tumor marker levels may detect recurrence of disease before any clinical or radiological evidence

- It is necessary to determine the tumor marker befor the primary therapy
- half-life
- lysis phenomenon

- **Monitoring of the effectiveness of antitumor therapy**

Frequency of determination

Recommendation of WHO

- During primary therapy – the time interval should be shorter than 1 month
- After primary chemotherapy– first six moths – every month

  second half year – every two months
- Next year– every 3/6 months
- Elevated level – a repeat estimate can be ordered within 2 to 4 weeks

Falsely elevated values

Tumor marker	Benign disorders
CEA	Liver inflammation, cirrhosis, pankceatitis
AFP	Lung inflammation, GIT, cirrhosis
TPA	Inflammations, jirrhosis pancreatitis
CA 15-3	cirrhosis, acute hepatitis, kidney disorders
MCA	Viz CA 15-3
CA125	Ovarian cysts, diseases of liverm kidney, pancreas
CA 19-9	Cirrhosis, cholelitiáza, chron.hepatitis, acute and chron.pankreatitis, billiary tract diseases, diabetes, cystic fibrosis
Ca 72-4	Benign breast tumor
PSA	Benign prostatic hyperplasia
hCG	Hydatidiform mole
2-microglobuline	Kidney disorders
TK	Interference herpes viry, B12 deficiency
SCCA	Lung inflammation, kidney and liver disorders,
Ferritin	inflammation, iron metabolic disorders
CYFRA 21-1	Urological disorder,s myoma, ovarian cysts

Preanalytical requirements

Most assays are performed in serum

- No special prean. requirements
- PSA
- NSE, LD
- catecholamines and their metabolites

Immunochemical methods!

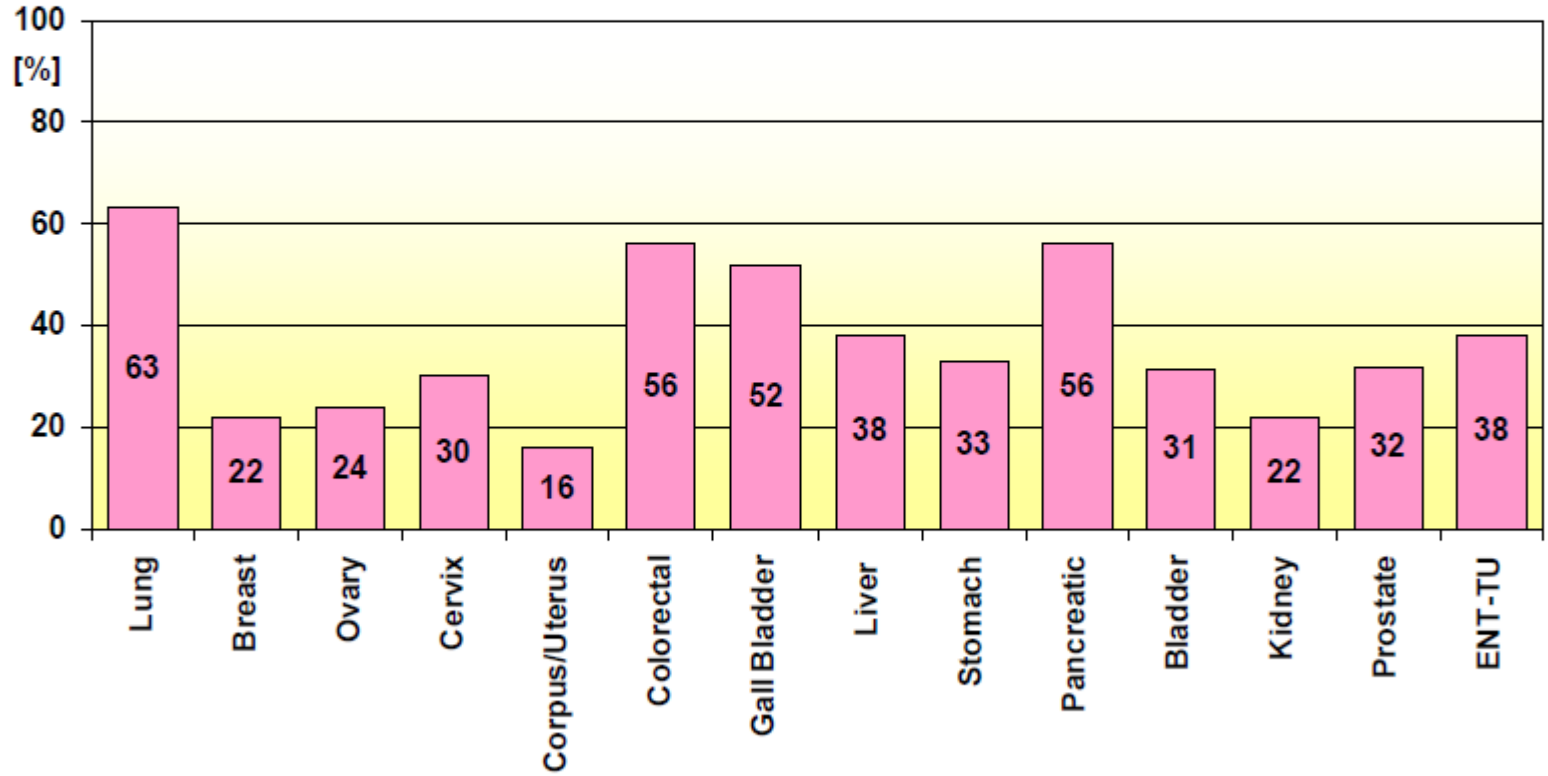
CEA (carcinoembryonic antigen)

- **Oncofetal glycoprotein occuring especially during fetal development in epithelium of GIT**

- **↑: *Ca GIT, pancreas, lung, breast**
  ***Ca ovarian, cervical, prostate**
  ***hepatitis, pancreatitis, chronic kidney failure , liver, nonspecific intestinal inflammation, TBC, autoimmune diseases**
  ***smokers**

- **In: monitoring after treatment of colorectal Ca and breast Ca , prognosis colorectal Ca**
- **< 5 ug/l**, half-life 14 days

Frequency of Release of CEA in Various Cancers



cut off CEA: 3 ng/ml

AFP
(α1-fetoprotein)

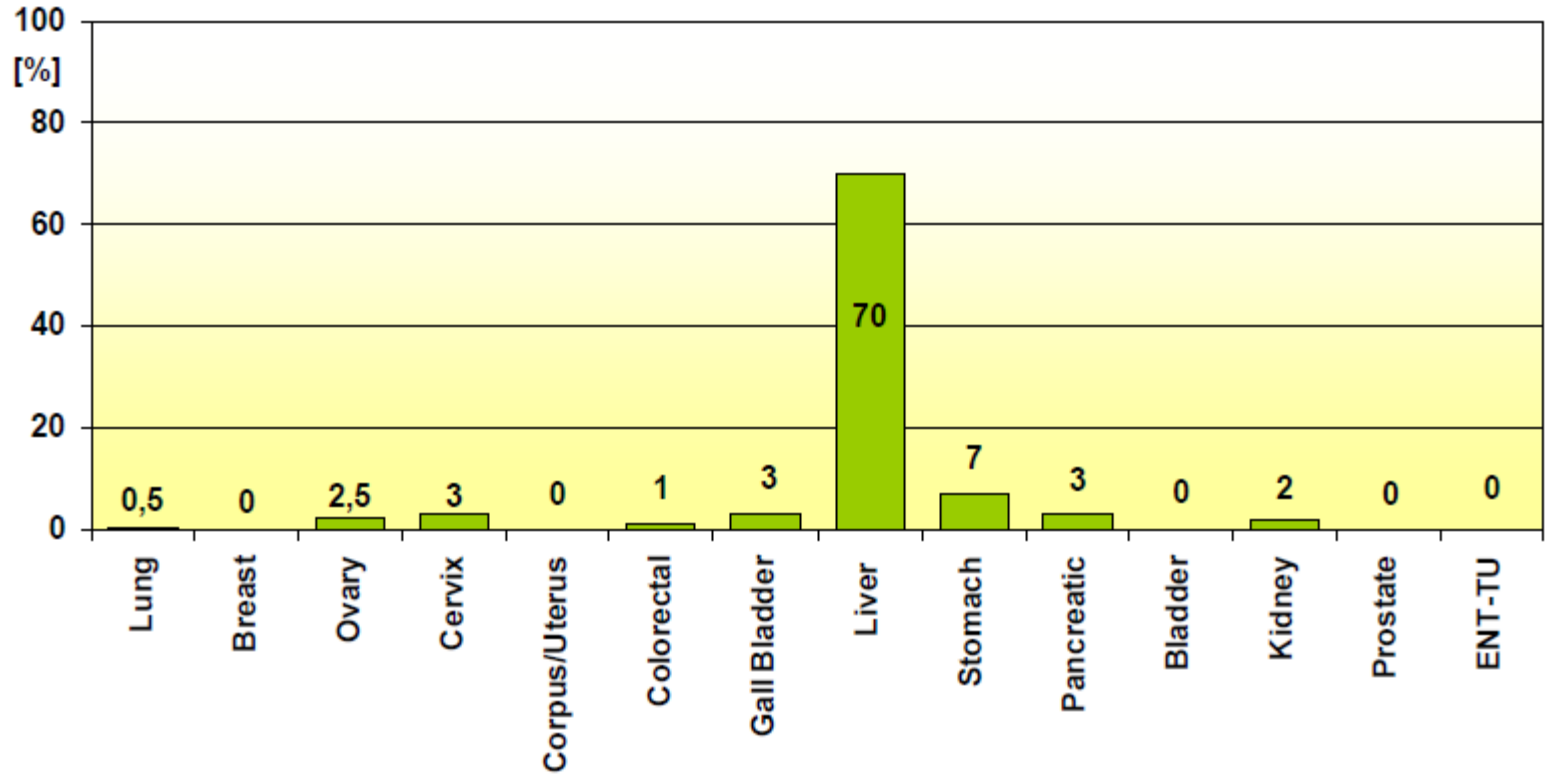
- Oncofetal protein produced during fetal live by yolk sac, and liver

- ↑: *primary hepatocellular Ca, metastases of other malignancies to the liver, germ cell Tu
  *GIT, pankreatic, breast, bronchial Ca
  * cirrhosis, hepatitis, chronic kidney failure
  *Down´s sy and spina neural tube during pregnancy

- In: dg and monitoring of primary hepatocellular Ca and germ cell Tu, monitoring of HbsAg and antiHCV positive patients

- ≤ 10 ug/l, half-life 3-6 days

Frequency of Release of AFP in Various Cancers



cut off AFP: 15 ng/ml

CA 15-3 (carbohydrate antigen 15-3)

- glycoprotein, during fetal live occurs in liver cells and bronchial epithelium, in adults in mammary gland cells
- ↑: *breast Ca , bronchogenic Ca
  *hepatocellular Ca , pancreatic, ovarian, dělohy, prostate *chronic diseases, AIDS, rheumatoid diseases
  *pregnancy (physiologically)
- In: monitoring breast Ca, not suitable for screening
- ≤ 30 kU/l, half-life 7 days

CA 19-9 (carbohydrate antigen 19-9)

- glycolipid of fetal epithelia of GIT, panceras and liver, in adult in very small concentrations in gastrointestinal tract and lung tissue

- ↑: *Ca pancreas
  *Ca ovarian (mucinous), gallbladder and biliary tract, liver, colorectal,breast, uterus,
  *biliary tract and liver diseases

- In: monitoring of Ca pancreas, colorectal Ca,
  dg a monitoring of gallbladder Ca, biliary tract and liver Ca

- ≤ 40 kU/l, half-life 5 days

CA 125 (carbohydrate antigen 125)

- glycoprotein of respiratory and digestive tract epithelium in fetal and adults

- ↑: *ovarian Ca (non-mucinous), colorectal Ca
  *breast, uterus, pancreas, liver, lung Ca
  *benign ovarian tumors, endometriosis, hepatitis, icterus, pancreatitis
  *pregnancy, in breast milk (physiologically)

- In: dg and monitoring of treatment ovarian Ca and colorectal Ca, complementary marker of pancreatic Ca

- ≤ 35 U/ml, half-life 4 days

HE4 (Human Epididymal protein-4)

- glycoprotein of respiratory and reproductive tract epithelium in fetal and adults

- ↑: *ovarian Ca (non-mucinous), breast Ca
  *sensitivity 76 %, specifity 95 % in combination with CA-125

- In: dg and monitoring of treatment ovarian Ca
- ≤ 140 pmol/l, ROMA i. ≤ 11,4 %. ROMA i. ≤ 29,9 % postmen

CA 72-4 (carbohydrate antigen 72-4)

- glykoprotein detected in fetal epithelium of esophagus, stomach and pancreas, in low concentration also in adults
- ↑: *Ca esophagus, stomach, ovarian Ca (mucinous)
  *Ca pancreas, uterus, colorectal, lung (NSCLC)
  *cirrhosis, stomac ulcers, GIT inflammation, acute pancreatitis
- In: monitoring of lung Ca, GIT and ovarian Ca
- ≤ 5 kU/l,

hCG (human choriogonadotropic hormon)

- glykoprotein synthesized by trophoblast of placenta during pregnancy. It is composed of two subunits α a β

- ↑: *hydatidiform mole, chorioCa, gonadal tumor (testes and ovary)
  *small cell lung Ca , Ca GIT, liver, kidney, breast
  *ovarian cyst
  *pregnancy (physiologically), post-menopausal

- In: dg and monitoring of mole and gonadal tumors

- ≤ 5 U/l non-pregnant (βhCG), half-life 1.5-2.5 days

TK (thymidine kinase)

- enzyme catalyses the reaction (thymidine → thymidine monophosphate)

  TK1, TK2

- ↑: *hematological malignancies

  *breast, lung, prostate, testicular, colorectal and bladder Ca

  *psoriasis, viroses, sarkoidosis, rheumatic diseases, anemia

- In: dg and monitoring of hemoblastosis a lymphomas

  complementary tumor marker for all malignant diseases

  9 U/l, half-life 2 days

NSE
(neuron-*specific enolase*)

- enzym of glycolysis (2-phosphoglycerate ⟶ phophoenolpyruvate), occurrence in neuroendocrine cells

- ↑: *Tu of neuroectodermal origin (neuroblastoma, medulloblastoma, retinoblastoma), neuroendocrine origin (small cell lung Ca, medullar Ca of thyroidea, carcinoid tumor, pheochromocytoma)
  *seminoma, renal cell Ca
  *lung and liver diseases, kidney failure

- In: dg a monitoring therapy of small cell lung Ca and other neuroendocrine and neuroectodermal tumors
  complementary marker for dg of seminoma
- **< 15 μg/l**, half-live1 day

LD (lactatedehydrogenase)

- enzym of glycolysis (lactate ↔ pyruvate). Non-specific marker. Concentration corelates with tumor size.

- ↑: *hematologic malignancies, especially acute leukemia, non-Hodgkin lymphoma
  * other tumors
  *↑ isoenzyme LD_5 conected with liver metastases
  * heart failure, hypothyroidism, anemia, lung and liver diseases (isoenzymes)

- In: monitoring therapy of acute leukemia, non-Hodgkin lymphoma, testicular Ca a Ewing Sa

- 1,67-3,17 μkat/l

PSA (prostate specific antigen)

- serin protease produced by prostate ephitelium
- ↑: *prostate Ca
  *other diseases of prostate (inflammation, ben.hyperplasia)
- In: screening, dg a monitoring therapy of prostate Ca, monitoring after radical prostactomy, monitoring of prostatic hyperplasia
- Cut-off 4 ug/l, half-life2-3 days

(f)PSA
(free prostate specific antigen)

- Product of normal healthy prostate and synthesized by the malignant prostate, makes up 15 % of total PSA

- ↑: *prostate Ca
  *colorectum Ca, lung, breast, adrenals, liver Ca
  *other prostate disorders

- In: screening, dg a monitoring therapy of prostate Ca , monitoring after radical prostactomy, monitoring of prostatic hyperplasia

- It is evaluated the ratio fPSA/PSA, half-life 7 h
  0-15 % malignant disorders, > 20 % benign disorders

- PHI (prostate health index – tPSA, fPSA, (-2)proPSA

ACTH (adrenocorticotropic hormon)

- Polypeptide hormon produced by the anterior pituitary gland. It stimulates secretion of glucocorticoids

- ↑: *pituitary tumors
  *ectopic production: small cell lung Ca, pancreas Ca, breast, GIT

- < 60 pg/ml
  half-life0,2 h

ADH
(antidiuretic hormon)

- a peptide hormone (9 AK) synthesized in the hypothalamus and stored at the posterior pituitary.It regulates the body´s retention of water by acting to increase water reabsorbtion in the kidney.

- ↑: *small cell lung Ca
  *pneumonia, porphyria

- 2-8 ng/l

PTH (parathormone)

- Peptide (84 AK) hormone secreted by the chief cells of the parathyroid glands. Synthesis and excretion is regulated by ionic calcium concentration. PTH acts to increase the concentration of ion calcium in the blood: stimulation of osteoclasts, increases reabsorption of Ca^{++} in kidney, and enhances the absorption of Ca^{++} in the intestine

- ↑: *parathyroid Tu
- *primary and secondary hyperparathyroidism

- 1,3-7,6 pmol/l, half-life 5 min

TG
(Thyroglobulin)

- Glycoprotein produced by the follicular cells of the thyroid containing iodin and carbohydrates

  determination of Tg can be affected by presence of anti-thyroglobulin antibodies, which can result in falsely high levels of Tg

- ↑: *certain types of thyroid cancer
  *Graves disease, inflammation of thyroid gland

- 33 ug/l, half-life1 day

Calcitonin

- Low molecular weight peptide (32 AA) hormon, synthesized by C cells of thyroid. Suppresses release of Ca^{++} from the bones.
- ↑: medullary carcinoma of the thyroid
  Ca lung, breast, renal, liver, carcinoid tumors
- In: monitoring of medullary carcinoma of thyroid, metastases
- ≤ 19 ng/l

Prolactin

- peptide (198 AK) hormon produced by pituitary gland . Secretion is regulated by endocrine neurons in the hypothalamus. It stimulates the mammary glands to produce milk, and has a wide range of other effects.

- ↑: *prolactinoma
  * prostate, breast Ca

- men 3 – 7,2 μg/l
  women 2,8 - 16 μg/l
- pregnant women ≤ 600 μg/l

TPA, TPS (tissue polypeptide (specific) antigen)

- nonspecific fragments of keratins produced by normal and malignant tissue, the degree of expression in tumors is remarkably high

  high sensitivity in comparison with specificity

  effectively markers for epithelial carcinomas

- ↑: *breast Ca, gallbladder Ca, colorectum Ca, lung Ca, kidney Ca

  *liver Ca, pancreas Ca, prostate Ca, thyroid Ca, ovarian Ca

  *hepatitis, cirhosis, DM

- In: monitoring therapy of breast Ca, GIT, bladder
- ≤ 85 U/l, cut-off 140 U/l, half-life 7 days

SCCA (squamous cell carcinoma antigen)

- glycoprotein receptor for Ig (hl. IgA)
- It is elevated in squamous cell carcinomas of head and neck, lung

- ↑: *lung Ca, cervical Ca, esophagus Ca, head and neck Ca
  *breast Ca
  *lung diseases, liver and kidney failure
  *pregnancy (physiologically)

- In: monitoring of lung Ca, head and neck Ca

- ≤ 1,5 μg/l, half-life 20 min

CYFRA 21-1

- an antigenic determinant of the cytokeratin
  it is expressed in normal, simple epithelium as well as in proliferating epithelium (lung, uterus,
  Higher organ specificity than TPA/S

- ↑: *non-small cell lung Ca
  *cervical Ca, breast Ca, bladder Ca, ovarian Ca, anal Ca
  *cirhosis, asthma, respiratory infections, chronic kidney failure

- In: monitoring cervical and lung Ca

- ≤ 3,3 μg/l, half-life 3 h

Ferritin

- The accute phase protein playing a role in sequestration and storage of iron (Fe^{3+})
- ↑: *acute leukemia, Hodgkin lymphoma, melanoma, neuroblastoma, hepatoma, MM
  *acute hepatitis, inflammation
- In: monitoring of Hodgkin lymphoma and melanoma
- men 48 - 708 pmol/l
  women 20 - 640 pmol/l
  half-life 2 days

β_2-microglobulin

- ligh chain constituent of HLA antigen, it is produced especially in B-lymphocytes and plasmacytes

- ↑: *leukemia, lymphomas, multiple Myeloma
  *inflammation, chronic kidney and liver diseases
  *after chemotherapy

- In: dg MM, prognostic value

- 1-2,3 mg/l

S-100 beta

- Protein expressed primarily by astrocytes, it is usually elevated due to central nervous system damage
- ↑: melanoma
- In: monitoring of melanoma, prognostic value
- Cut-off 0,1 ug/l

Potential new tumor markers

Proteins and oncoproteins–produkts of mutated genes, genů, that are important for cell survival, their differrentiation and metastasis

- **Regulation of cell cycle**- cyclins
- **Apoptosis**–Bcl-2 protein, sFas, protein-product of mutated gene p53
- **Signal transduction**-c-erbB-2 (Her-2/neu), EGRF, IGF, TNF-α
- **Adhesion**-ICAM-1, VCAM-1
- **Angiogenesis**–inhibitor angiogenesis-angiostatin, angiogenin, trombospondin

Catecholamines and their metabolites

epinephrine, norepinephrine and dopamine and
serotonin belong to the group of biogenic amines.
They act as neuromodulators in the central nervous system and as hormones in the blood circulation

- Physiologically relevant catecholamines are epinephrine, norepinephrine and dopamine.
- Epinephrine (E) has been considered a classic example of a hormone and norepinephrine (NE) a neurotransmitter but both function reciprocally.
- E is produced primarily by the chromaffin cells of the adrenal medulla and NE by the sympathetic neurons but they both have similar structures and biological actions.

- very short half-life – 2 min

- NE and E are metabolized extracellulary by COMT to normetanephrine and metanephrine, respectively.

- Sequential action of COMT and MAO leads to the main metabolite excreted in the urine, 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA).

- dopamin is metabolized by o-methylation and by deamination to homovanilic acid (HVA)

The abnormal production or secretion of catecholamines is typical in neuroendocrine tumors (pheochromocytoma, neuroblastoma, paragangliomas)

The determination of levels of catecholamines a their metabolites enables an early detection of tumors and monitoring of treatment.

Common radiodiagnostic examinations (sono, CT, NMR, PET) serve for confirmation of laboratory tests and localization of tumors.

- the production of E and NE is not specific only for pheochromocytoma
- silent pheochromocytoma – sporadic releasing of catecholamines
- free metanephrines are produced continuously within pheochromocytoma tumor cells and independently of catecholamine release – great importance for detection of pheochromocytoma

⬇

Development of new procedures for measurement of plasma free metanephrines

interpretation of results

x

false positive

renovascular hypertension, hypotension, hypovolemia, hypoglycemia, stress, sepsis, dumping syndrom, sleep apnea

different preanalytics procedures

Determination of A, NA, VMA, HVA, 5-HIAA

diet: bananas, oranges, grapefruits, tomatoes, nuts, cheese, chocolate, cacao, tee. coffee, alcohol, vanilla, foods with vanillin

medikaments:

betablockers
alfablockers
antihypertensives
inhibitors MAO
disulfiram
antibiotics
benzodiazepins
chinin, chinidin
solatol
chlorpromazin
labetalol
triamteren
methyldopa
mandelamin

Advantage of plasma free metanephrines determination:

blood collection– few minutes calming, vein cannulation is necessary

results – not affected by food (caffeine)

drugs (tricyclic antidepressants, betablockers)

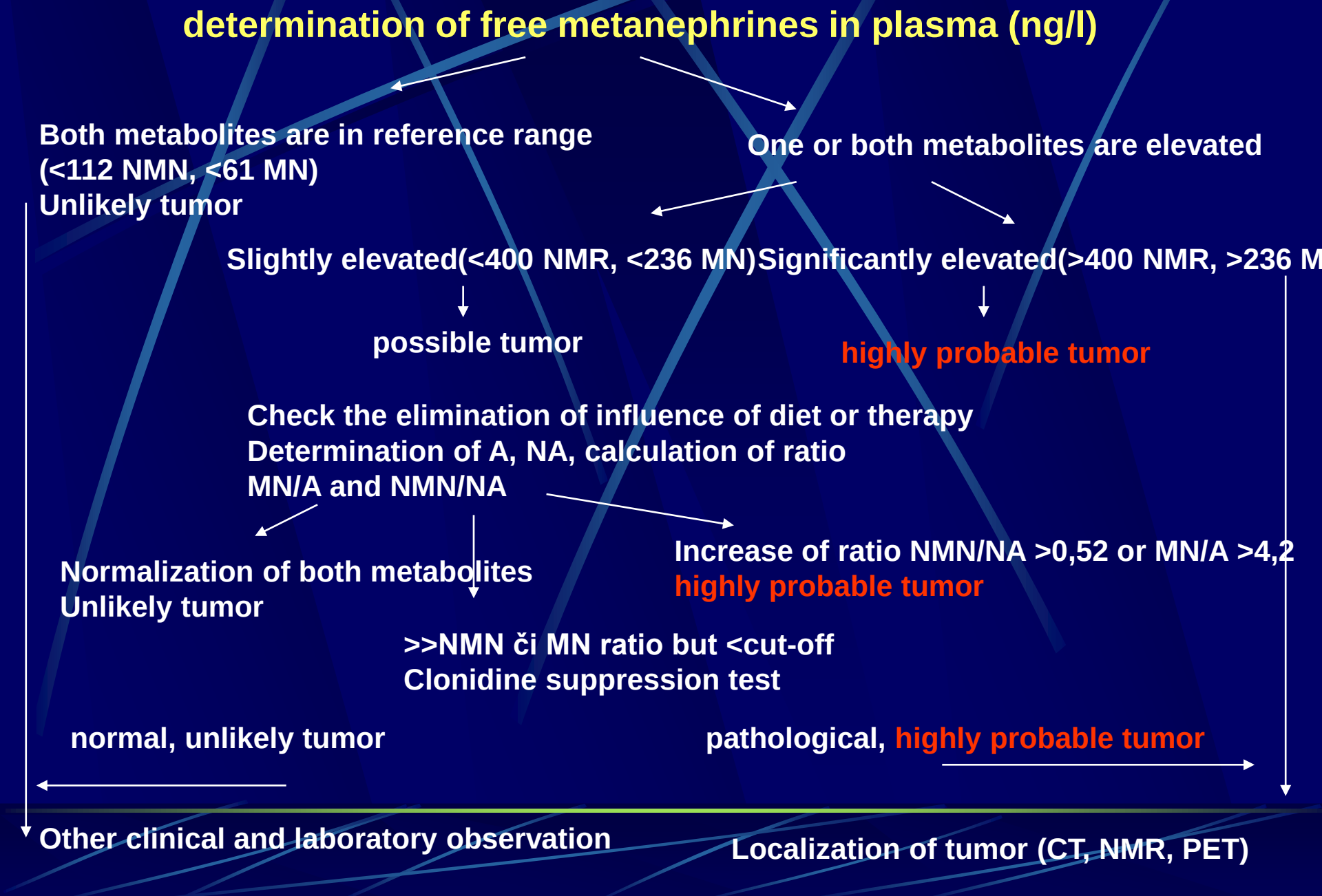
Disadvantage of plasma catecholamines determination:

blood collection– long-term bed rest (more than 12 hours)

results – can be affected by various food (diet necessary), drugs, and physical

and psychological stress

Diagnostic schema for pheochromocytoma



Patient, female, born 1945

Metanephrine	41.8	(0-61) ng/l
Normetanephrine	72.1	(0-112) ng/l
Index MN/E	0.38	(0-4,2)
Index NMN/NE	0.05	(0-0,52)
Epinephrine	109.3	(0-84) pg/ml
Norepinephrine	1342.6	(250-420) pg/ml

The values do not indicate presence of pheochromocytoma (secondary stress)

Patient, male, born 1953

Metanephrine	1154.2	(0-61) ng/l
Normetanephrine	2539.3	(0-112) ng/l
Index MN/E	33.46	(0-4,2)
Index NMN/NE	10.88	(0-0,52)
Epinephrine	34.5	(0-84) pg/ml
Norepinephrine	233.4	(250-420) pg/ml

Catecholamines normal, free nephrines increased, indexes increased

Suspect pheochromocytoma of adrenal localization.

Female born 1946

Glukóza	**7,75**	**mmol/l**	**(4,6-6,4)**
ALP	1,35	ukat/l	(0,66-2,20)
ALT	0,49	ukat/l	(0,17-0,63)
AST	0,38	ukat/l	(0,16-0,63)
GGT	0,93	ukat/l	(0,14-0,78)
Amylasa	0,73	ukat/l	(0,30-2,28)
Celk. bílkovina	**59,94**	**g/l**	**(65-85)**
Albumin	36,1	g/l	(35-53)
BIL – celk.	2,9	umol/l	(2-17)
Ca – celk.	2,23	mmol/l	(2,05-2,54)
Cholinesterasa	125,11	ukat/l	(88,7-215,3)
Cholesterol	**5,54**	**mmol/l**	**(3,4-5,0)**
HDL	**0,73**	**mmol/l**	**(0,9-1,42)**
LDL	**3,95**	**mmol/l**	**(1,5-3,0)**
TRIGL.	**4,14**	**mmol/l**	**(0,7-1,7)**
Kretinkinasa	0,53	µkat/l	(0,41-3,24)
Kreatinin	65,95	umol/l	(42-80)
Urea	6,97	mmol/l	(2,8-8,0)
Kys. močová	334,9	umol/l	(200-420)
Fe	12,56	umol/l	(7,2-29)

K^+	**3,74**	**mmol/l**	**(3,8-5,0)**
Na^+	143,5	mmol/l	(137-146)
Cl^-	106,8	mmol/l	(97-108)
Mg	0,74	mmol/l	(0,66-0,91)
P	1,19	mmol/l	(0,65-1,61)
Laktát dehydrog.	**2,07**	**ukat/l**	**(3,5-7,0)**

CYFRA21-1	3,24	ug/l	(0-3,3)
NSE	8,57	ug/l	(0-17)
CEA	5,34	ug/l	(0-9,2)
CA19-9	7,15	kU/l	(0-35)
CA125	21,4	kU/l	(0-30)
CA 153	10,5	kU/l	(0-32,4)
CA 72-4	0,802	kU/l	(0-8,2)
S100	0,064	ug/l	(0-0,11)

Mamog. – invasive ductal carcinoma

13.7.2011 – left breast ablation

X-ray lung, USG liver– negative

SCINTI skeleton – higher activity in the first ribs

6 series chemotherapy

1-2/2012 radiotherapy

After the radiotheraphy – tretment by bisphosphinates + HT

CEA 2,6 ug/l, CA 15-3 12,6 kU/l

10/2012

CEA 5,2 ug/l, CA 15-3 13,1 kU/l

CT - neg., SCINTI – lower activity in ribs

1/2013

CEA 11,98 ug/l, CA 15-3 34,8 kU/l

CT – hypodensity in liver 11x7 mm, lungs neg.

SCINTI – stávající s pokleseem aktivity

from March 2013 hormon therapy Faslodex+ Xgiva do 12/2013

1/2014

CT – retrocaval lymp node, tumor lesions in both lung wings

CEA 8,74 ug/l, CA 15-3 19,0 kU/l

Female born 1968

Glu	4,39	mmol/l	
ALP	1,58	ukal/l	
ALT	0,29	ukat/l	
GGT	0,25	ukat/l	
C.bil.	72,27	g/l	
Alb	43,96	g/l	
Urea	4,50	mmol/l	
Krea	72,34	umol/l	
LD	3,11	ukat/l	(3,5-7,0)
K+	4,19	mmol/l	
Na+	140,6	mmol/l	
Cl-	104,0	mmol/l	
CRP	10,28	mg/l	
CEA	0,48	ug/l	
CA19-9	13,06	kU/l	
CA125	12,6	kU/l	
CA 15-3	34,2	kU/l	(0-32,4)

Mammog.: cyst

Case study - hypertension

Male – 50 years, regular check, after two years
185 cm, 90 kg, BMI = 26.3
BP 150/100, P 96/min, no pathological changes, EKG normal
Recom.: urine + sediment, Retinal examination, FW, KO, liver enzymes, creatinine, uric acid, Na^+, K^+, Cl^-, Ca^{++}, glycemia, lipids, TSH, fT4, PSA
Therapy: Metropolol twice daily, slim
Check 3.11.:
BP 170/105, P 90 min, sweating 1-2 weekly
Check 18.11.:
BP 150/95, P = 80/min, no sweating, pressure in liver areas
Therapy: Metropolol, Amlodipin in morning
Check 30.11.:
BP 135/85, P = 84/min, check in a month
Check 15.12.
BP 150/95, P = 90/min, twice increased strong sweating without accompanying strain, booked Holter's monitor
Check 15.2.
Variable BP up to 190/120, abdomen USG – susp. enlarged right adrenal gland
VMA in urine ↑, week leukocytosis, CT – hypertrophy of right adrenal gland

Early pheochromocytoma detection
Minimal symptoms
Usage of beta-blockers worsened hypertension

Neuroblastoma

Boy 2.5 months, SVD, 4 kg, 51 cm, well thriving, no illness

9th week after birth enlarged abdomen

Found hepatosplenomegalia – transferred to FH Motol, suspected metabolic syndrome

Proved hepatosplenomegalia, developing deposit in liver, and clusters of unripe cells in bone marrow – suspected neuroblastoma

Laboratory exam:

HVA	298 mmol/mol creatinine
VMA	246 mmol/mol creatinine
DOPAC	1.2 mmol/mol creatinine
5-HIAA	1,4 mmol/mol creatinine
AST	2.95 ukat/l
GMT	3.37 ukat/l
LD	14.0 ukat/l
Total protein	34.9 g/l
Albumin	26.1 g/l
IgG	1.8 g/l

Antitumor therapy, 5 series

HVA	14,2 mmol/mol creatinine	(1,05-2,0)
VMA	6,8 mmol/mol creatinine	(0,4-4,0)
DOPAC	0,9 mmol/mol creatinine	(1,0-1,3)
AST	0,75 ukat/l	
LD	5,8 ukat/l	

2.5 year old girl, SVD 4.2 kg, 53 cm, well thriving, no illness
After fall from staircase (no consequent problems) tired, feeling cold, no appetite, insomnia
Then occurrence of veins on upper eyelids, next day hematoma
Ophthalmology check revealed retinopathy
Observed hepatomegaly, palpable resistance in right part of abdomen
Sono – observed resistance in the area of right adrenal gland

Check:

LD	**180.4 ukat/l**	
VMA	**10.9 mmol/mol creatinine**	**(0.4-4.0)**
HVA	**97 mmol/mol creatinine**	**(1.05-2.0)**
DOPAC	**15.2 mmol/mol creatinine**	**(1.0-1.3)**
5-HIAA	**9.6 mmol/mol creatinine**	**(2.0-2.6)**

Head CT: metastatic process in right orbit
Abdomen CT: neuroblastoma of right adrenal gland, blood perfusion
Skeleton RTG: diffuse, thinner skeleton

Pacient 1936

5 years he is being treated for depression, didn´t feel well
uses SSRI
Observing visual impairment – visual field constriction, 8 → 3

Asked for help on phone

Headaches negativ, observed decrease in performance and worse stress tolerance

Admitted to MR + biochemistry

Biochemistry:

Glucose	**6,6 mmol/l**
PSA	**< 0,003 ug/l**
testosterone	**4,35 nmol/l**
cortisol	**271 nmol/l**
Prolactin	**> 200 ug/l**

MR:

Sellar expansion with extrasellar propagation and ingrowth to pr. ACC without oppression chiasma opt. and visual pathways

Carcinoid

Tumours producing mainly serotonin, and its metabolites, however, other biol. active
compounds (chromogranin A, histamine, insulin, glucagon, …) were observed

Variable clinical symptoms – called carcinoid syndrome (10-30 %)

flush syndrome, skin problems, diarrhoea, cardiatic symptoms, abdominal pain
bronchospasma, hypotension

Diagnosis - 5-HIAA estimation

Patient, female, born 1963

For half a year observed - intermitent diarrhoea
CT of pancreas / negative
Pancoloscopy – diffused distinct vein depiction, no pathology
After 2 month UC of epigastrium – non/characteristic changes on the border of body and pancreatic cauda
Check food allergies
Observed allergy to apples – result: focal pancreatitis and food allergy

After 2 months again UC of epigastrium, persistent diarrhoea, unclear observation
CT of pancreas – focal pancreatitis with partial thrombosis, unobstructive in
v. portea
Hospitalization, started anticoagulation treatment, MRI, UC – Thrombus size 2.6 cm
Laboratory check – everything in reference (amylases, KO, urine, CA 19-9, CEA, 5-HIAA)
After treatment reduction of reported health problems size of thrombus increased to 5 cm
In one year apparent dilated veins medial from spleen, splenomagaly, thrombus as a soft tissue deposit

Patient transferred to FH Motol with diagnosis of portal hypertension with
pre-a intrahepatal blockade, unclear observation in pancreas
Per-surgery diagnosis – pancreatic adenocarcinoma with metastasis in lymph node tumourous thrombus in v.portale

– final diagnosis> carcinoid

Patient with unusual case of thrombosis on lienal and portal vein with complicated and long lasting search form tumour ethology (biochemical check all the time negative)

Patient, female, born 1949

Admitted fro hospitalization du to diarrhea, loud systolic mourmour, liver
3 cm over rib arc, facial telangiectasias, other observations normal
Subjective symptoms: worsening diarrhoea, seizures of dyspnoea , weight loss
Gastroscopy and colonoscopy negative
Repeated liver UC – deposit in liver, non metastatic

Admitted to GM
after UC, and kardioechographic check
diagnosed - suspection of generalized carcinoid
Laboratory: 5-HIAA 810 umol/day (47 umol/day) and
Serotonin 3.17 umol/day (1.4 umol/day)
Total protein 56 g/l
albumin 34 g/l
Liver enzymes increase

Paraprotein

- production of a monoclonal immunoglobulin molecule
- produce by proliferating clone of plasma cells or B cells
- Monoclonal immunoglobulins are usually complete imminoglobulins but may be isolated light chains or heavy

Monoclonal gammopathy (MG)

⇓

Malignant disease in which an abnormal protein (monoclonal immunoglobulin) is produced by plasma cells, a type of white blood

Monoclonal product of malignant cell is in each patient individually specific

Changes in concentration of monoclonal protein in serum can be in the same mohou být u téhož jedince indikátorempočtu produkujících nádorových buněk

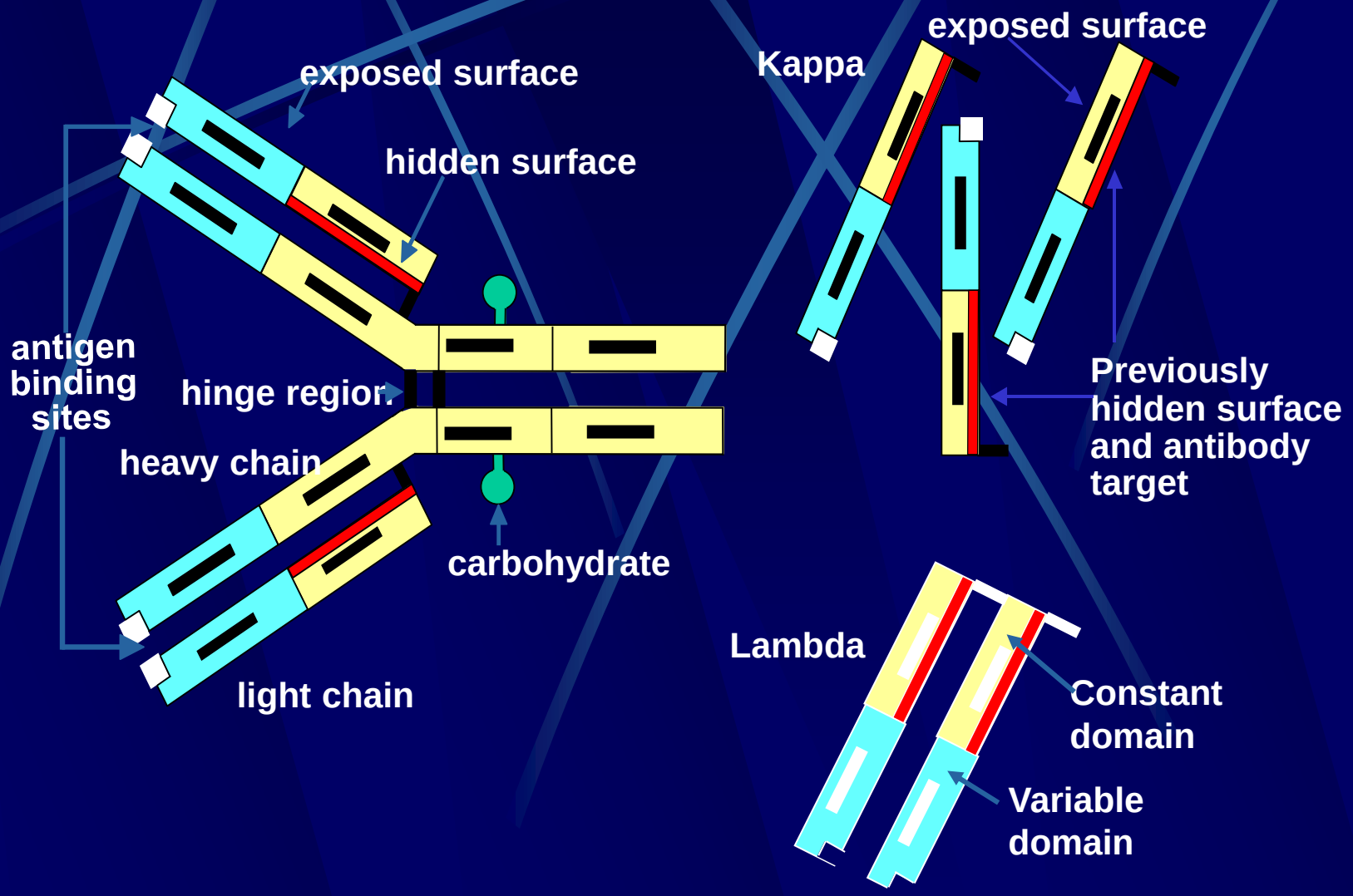
Between monoclonal gammopathy is included:

- Multiple myeloma (MM)
- Nonsecretory multiple myeloma (NSMM)
- Smoldering myeloma (SMM)
- Primary systhem L – amyloidosis (AL)
- Waldenström´s macroglobulinemia (WM)
- Monoclonal gammopathy of undetermined significance (MGUS)

Immunoglobulin molecule

- Immunoglobulin molecul (Y-shape protein) consists of two identicaly heavy chains (α, γ, μ, δ, ε), and two identical light chains (κ or λ). The type of heavy chain defines the class of immunoglobulins
- Light chains are connected to heavy chains by disulfide bondss
- Each tip of the „Y“ contains a paratope, which is specific for one epitope on a antigen, allowing these structures to bind together
- Light chains are produced in comparison to heavy chains in 40 % excess
- Free light chains are secreted into the urine as Bence-Jones protein

Complete molecule of IgG



Determination of free ligh chains (FLCs) immunoglobulins in serum is used in diagnosis and monitoring of monoclonal gammopathy

•Half-life of light chains is different

kappa	2 – 4 h
lambda	3 – 6 h
oligomerní formy	3 – 6 h

- Half-life of complete molecule of immunoglobulins

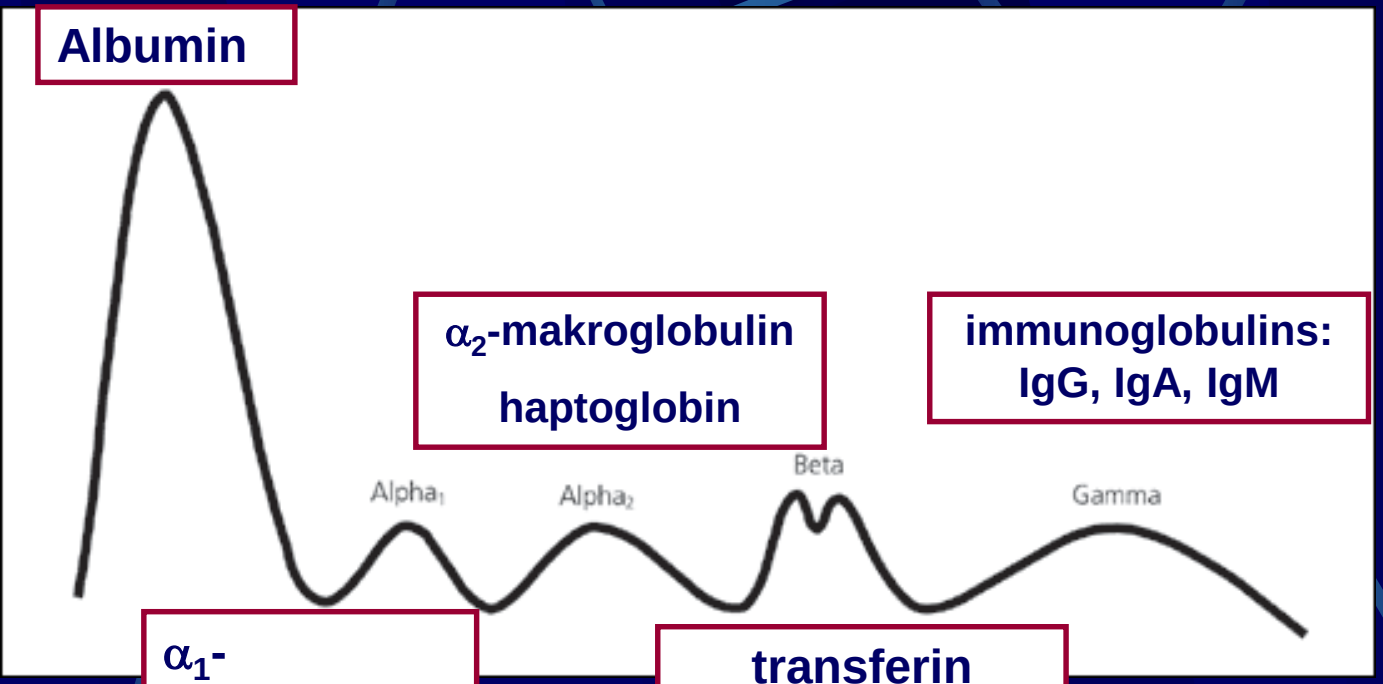
IgG – 21 days
IgA – 10 days
IgM – 7 days

⇒ enables faster monitoring of treatment

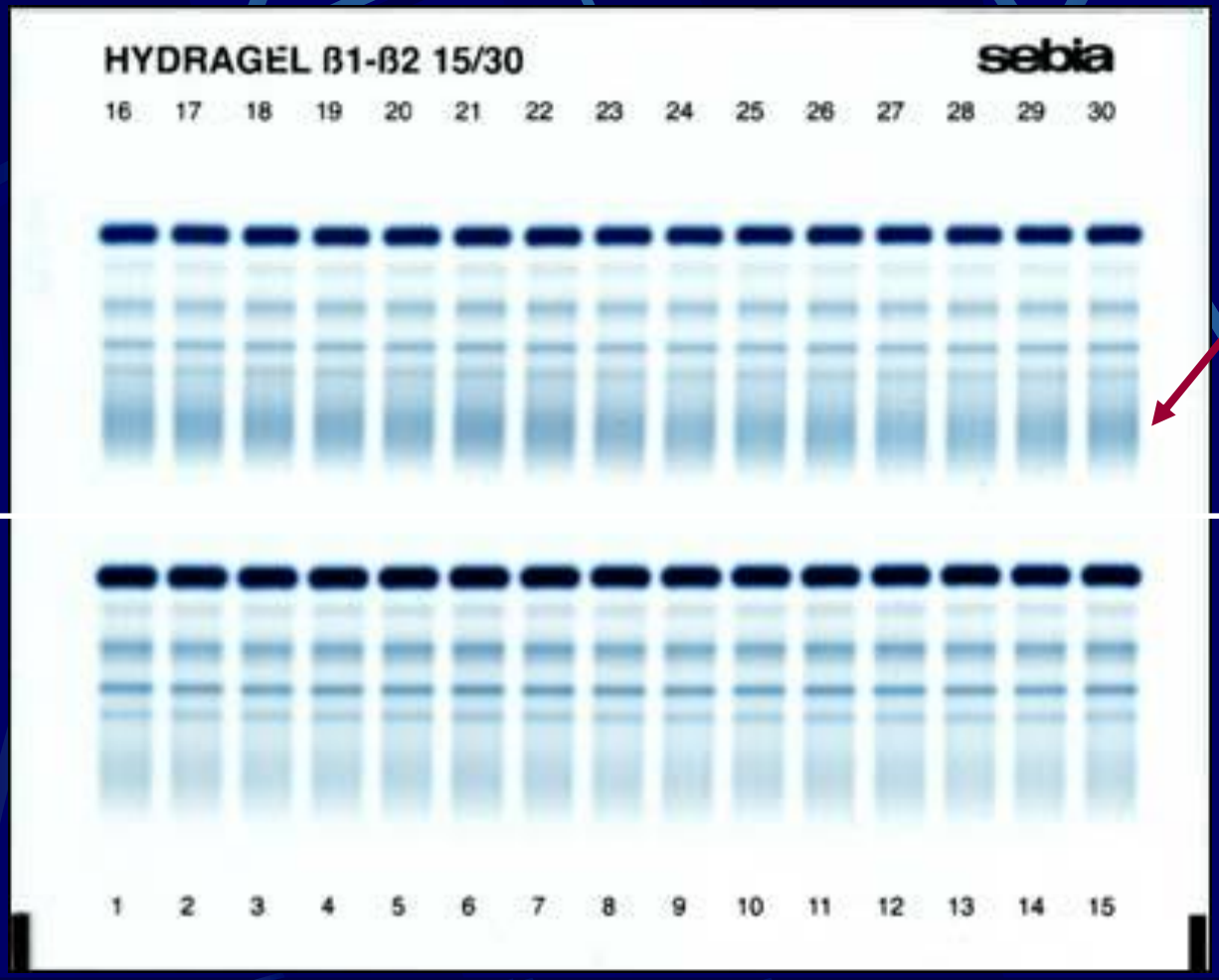
Concentration and indexes κ/λ (Bradwell a spol. 2001)

	Free light chains in serum	Free light chains in urine
κ	7,3 (3,3 – 19,4) mg/l	5,5 (0,39 – 15,1) mg/l
λ	12,7 (5,7 – 26,3) mg/l	3,17 (0,81 – 10,0) mg/l
κ/λ	0,6 (0,26 – 1,65)	1,73

Serum protein electrophoresis



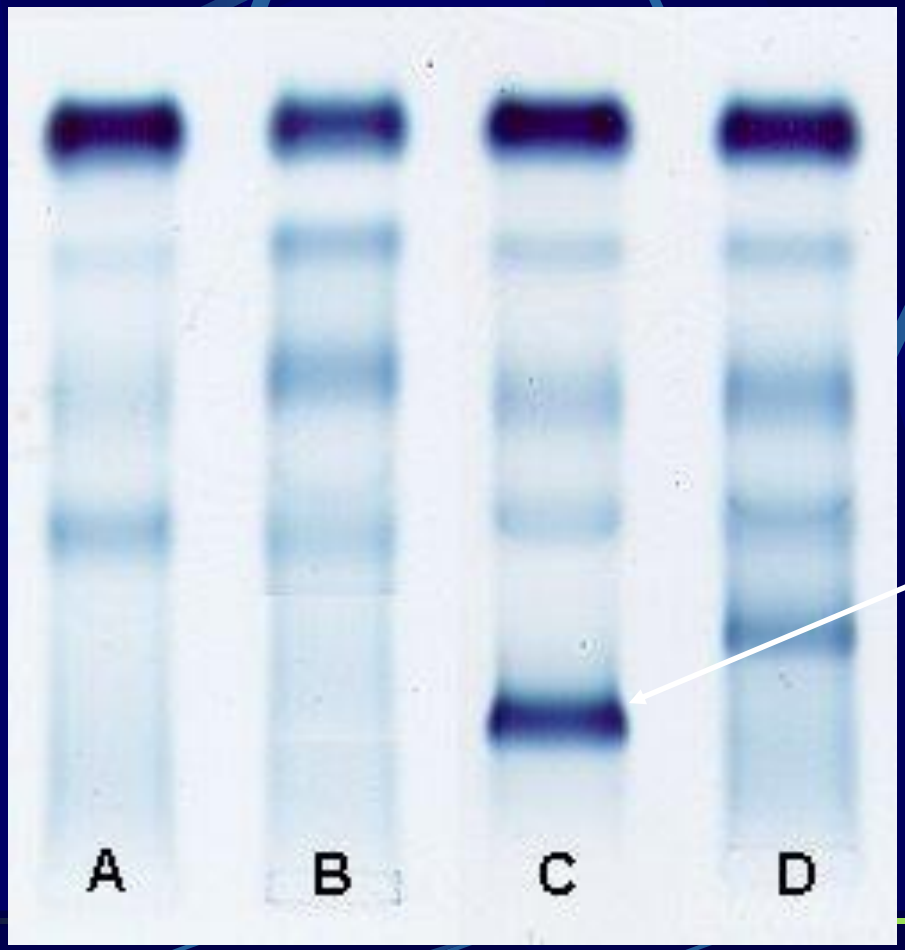
Serum protein electrophoresis



hypergamma-globulinemia

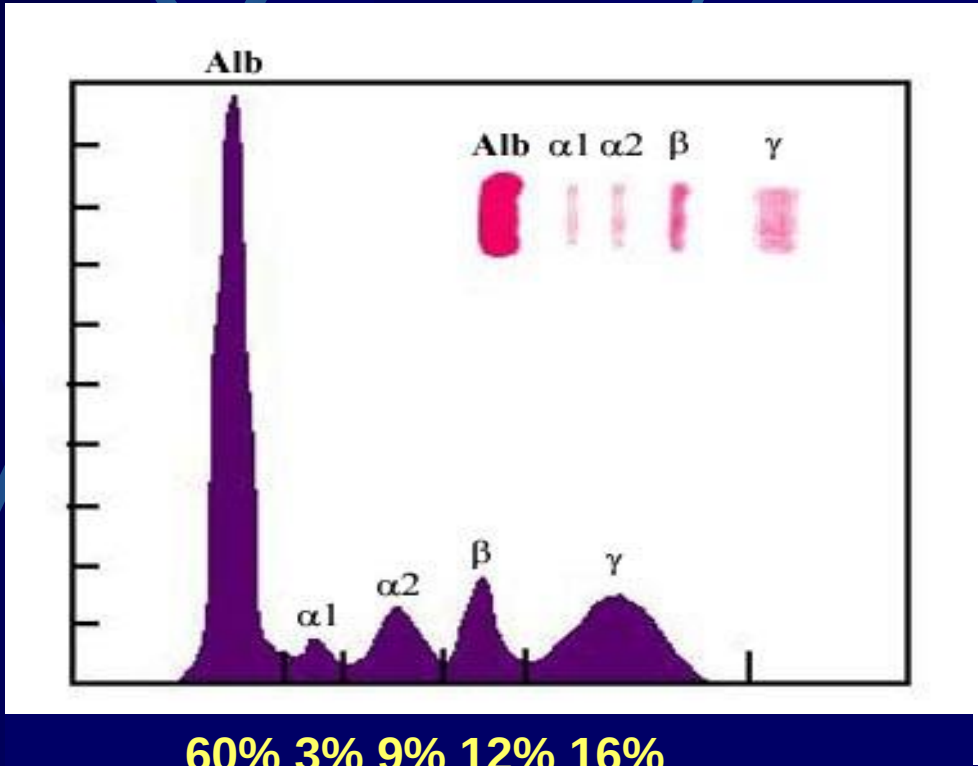
healthy patient

Serum electrophoresis

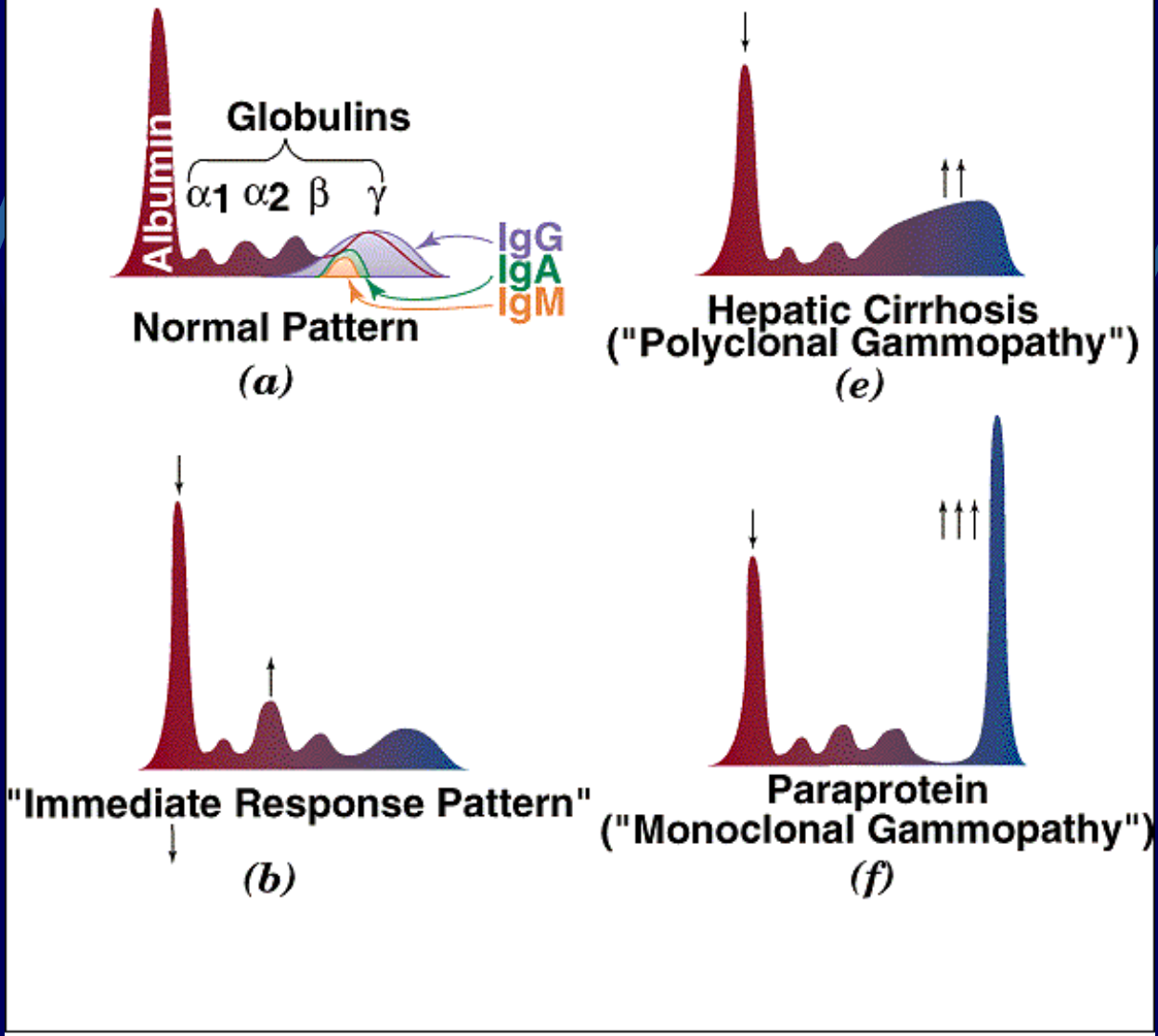


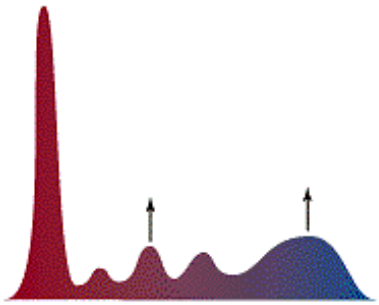
A. Physiological finding
B. Acute illness
C. paraprotein
D. Fibrinogen in plasma

Denzitometric record of electrophoresis



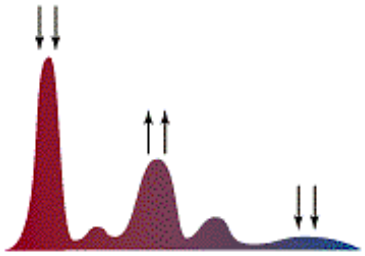
60% 3% 9% 12% 16%





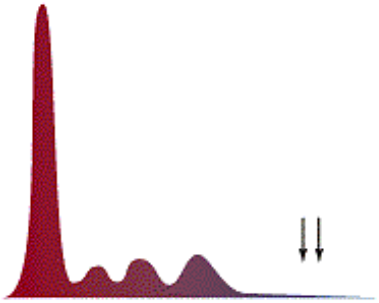
"Delayed Response Pattern"

(c)



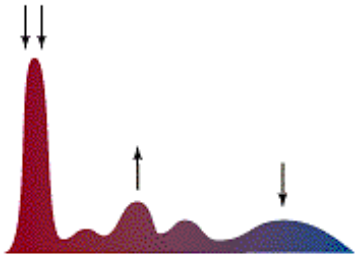
Nephrotic Syndrome

(g)



Hypogammaglobulinemia

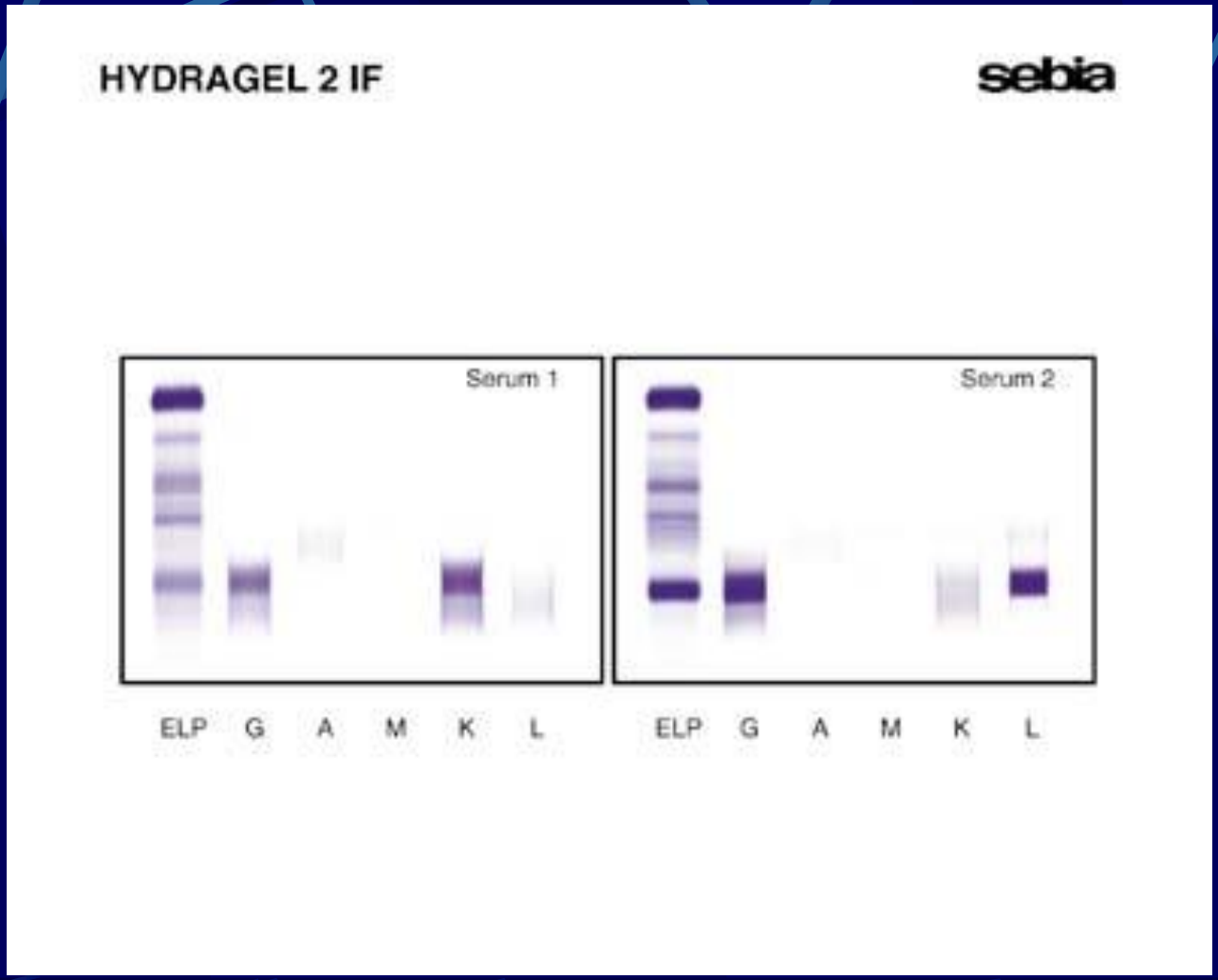
(d)



Protein-losing Enteropathy

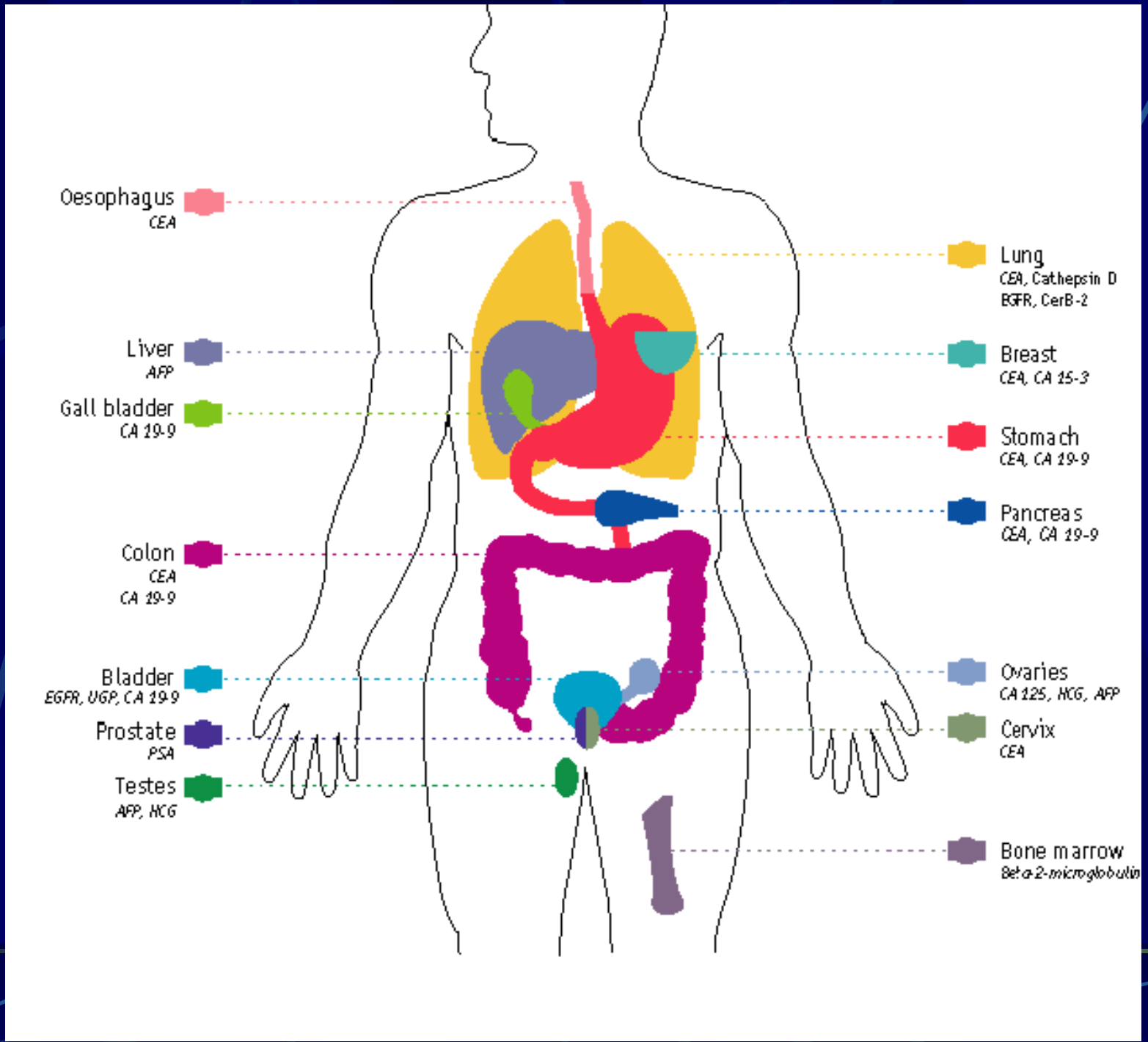
(h)

IMMUNOFIXATION
- type of paraprotein (*monoclonal Ig*)



Common clinical uses of some tumor markers[2 5 9]

Malignancy	Tumor marker (s)	Tumor marker detection method
Adrenal carcinoma	Steroids, Catecholamines	Serology
Breast	CA 15-3, CA 27.29	Serology / Tissue IHC
	ER / PR / Her-2neu	Tissue IHC
Carcinoid	5-HIAA	Serology / Urine
Colorectal, stomach, pancreas	CEA, CA 19-9	Serology / Tissue IHC
Choriocarcinoma	β-hCG	Serology / Tissue IHC
Germ cell tumors	AFP,β-hCG	Serology / Tissue IHC
	LDH, PLAP (Seminoma)	Serology
Hepatoma	AFP	Serology / Tissue IHC
Lymphomas	LDH	Serology
	Cytogenetic alterations	Genetic analysis
Melanoma	Tyrosinase	Serology
Myeloma	Immunoglobulins	Serology
Ovarian	CA 125	Serology / Tissue IHC
Prostate	PSA	Serology / Tissue IHC
Sarcomas	Cytogenetic alterations	Genetic analysis
Thyroid	Thyroglobulin	Serology / Tissue IHC
	Calcitonin (medullary carcinoma)	Serology


Oesophagus
CEA
Liver
AFP
Gall bladder
CA 19-9
Colon
CEA
CA 19-9
Bladder
EGFR, UGP, CA 19-9
Prostate
PSA
Testes
AFP, HCG
Lung
CEA, Cathepsin D
EGFR, CerB-2
Breast
CEA, CA 15-3
Stomach
CEA, CA 19-9
Pancreas
CEA, CA 19-9
Ovaries
CA 125, HCG, AFP
Cervix
CEA
Bone marrow
Beta-2-microglobulin