THE NUCLEAR MEDICINE

Introduction

The nuclear medicine is one kind of imaging methods. The imaging techniques consist of different radiological and isotopic examinations.

The nuclear medicine is: the using of radioactive isotopes in the diagnostic and in the therapy.

The specialty of nuclear medicine has its roots in the last 5 years of the nineteenth century, when the phenomenon of radioactivity was discovered by Bequerel in 1896 (eighteen ninety six). There was a hungarian men, Hevesy György, who was the first in using the radioactive material as a tracer.

The artificial radioactivity was discovered in 1930′s, almost every element could be converted to a radioactive form by changing its nuclear composition. The new radioactive elements eg. Technetium 99m, Indium 111 (one-one-one), and Iodine 131 (one-three-one) were rapidly introduced into the medical diagnosis and therapy.

The development of instruments took much longer period. It was not until 1950′ s (ninteen fifty′s) that scintillation detectors were developed, first for use in nuclear physics, then transferred to medicine. The scintillation detector is very efficient in detecting certain types of radiation, and has played crucial role in the development of nuclear medicine.

The structure of the nuclear atom

Radioactivity is the spontaneous disintegration (decay) of the nucleus of a radioactive atom. The nucleus is the central heavy part of the atom. In the decay event, several kinds of radiation may be emitted from the nucleus.

Atoms with the same number of protons but differing number of neutrons are called isotopes of that element. Only certain combinations of protons and neutrons are stable, the others are radioactive.

Units of measurement

The activity of a radioactive element is usually given in disintegrations per second, this is the dps.

The other important aspect of radioactive decay is the half-life, which is defined as the time required for one-half of the atoms in a group of radioactive atoms to decay. The half-life is unique physical property of a radioactive isotope and is a constant for any given isotope. The half-life cannot be modified by the external conditions.

The energy of the radiaoctive decay is the given energy during the radioactive desintegration, it is measured by electron volt, usually expressed in multiples of a thousand (keV) or millions (MeV).

Radioactive decay and emission

There are three basic kinds of radiations: alpha, beta and gamma radiation.

Gamma rays are really electromagnetic radiation with properties similar to light-rays, radio waves and X-rays. Gamma radiation is physically similar to X-rays, but it comes from the nucleus of the atom. Gamma-rays are very penetrated and easily pass through tissue. In nuclear medicine radioisotopes which emit gamma-rays are administerd to the patients. The gamma-rays emitted by decaying radioisotopes in the organ are detected externally with extremly sensitive detectors, which detect individual gamma-photons.

The most widely used radioisotope in nuclear medicine is **technetium 99m**. The *m* refers to a metastable state of the nucleus which decays with a very short half-life: 6 hours to the more stable Tc 99 by emitting a gamma-ray of 140 keV.

The used isotope must emit gamma-rays to make it detectable outside the patient and its physical half-life and energy should be short and relative small to minimize radiation exposure to the patient.

Beta particles are really high-speed electrons emitted by certain radioactive isotopes, such as I 131. The energy of these electrons ranges from a few keV to several MeV. Each different beta-radioactive nuclide emits a characteristic spectrum of electrons e.g. I 131 emits beta-particles with a range of energies up to 608 keV. The range of beta-particles in tissue is also only a few millimeters, so external detection of beta-particles is almost impossible. The biological damage to tissues is high, as indicated by the efficiency of thyroid ablation with I 131.

There are an other type of beta-decay when the isotope produces a positivly-charged beta-particle, the positron. Proton-rich nuclei emit positrons. F 18 is the typical example of this decay. Common other examples are O 15, N 13 and C 11, too. The positron is an anti-particle and when it slows down, it may combine with a normal electron, whereby their mass is converted into electromagnetic energy in a process known as annihilation. The result is two energetic photons emitted simultaneously in opposite directions each with an energy of 511 keV. These photons are similar to the third form of decay, the gamma-rays. These isotopes are used for the positron emission tomography, the so-called PET examinations.

Detection of nuclear radiation

It is the base of the detection of gamma-rays, which leaving the patient may undergo photoelectric interaction in the detector. Thus the detector "sees" the gamma-rays coming from the patient.

Scintillation detectors are compounds which emit visible light when struck by nuclear radiation. The scintillation detectors most often used in nuclear medicine consist of a single crystal of sodium-iodide. While pure sodium-iodide is not a good scintillator, the addition of a few tenths of one percent of thallium iodide increases the light emitted. It produces about 30 visible light photons per keV if gamma-ray energy deposited in the crystal. The visible light is observed by a photomultiplier tubes, which convert the visible light flashes from the scintillator to an electronic pulse. The size of

the electronic pulse, in volts, is directly proportional to the amount of energy of the gamma-ray deposits in the crystal.

Radioisotope imaging

The basic type of the imaging devices in nuclear medicine is the so-called **gamma-camera**. The basic concept of the gamma-camera was developed by Anger in 1950′s.

The detector consist of a sodium ioded scintillation crystal 3-16 inches in diameter and one-half inch thick. For the imaging we need so-called collimators, which are the lenses of nuclear medicine instrumentation. They usually constructed from lead, which absorbe the scattered gamma-rays. The gamma-cameras have paralel-hole collimator for Tc detection. Only the perpendicular gamma-rays coming from an organ can go through to the collimator and interact with the detector material, the others are absorbed. The crystal is "looked at" by hexagonal array of photomultiplier tubes. (The cameras have 19 tubes or 37 tubes.) The visible light produced in the scintillator is shared by all the photomultiplier tubes. The pulse outputs the each of the photomultipliers are sent to two electronic circuits, which analyse the pulse height and the pulse position, and the dots flash on the oscilloscope. The analogous pictures of the oscilloscope are photographed by Polaroid or X-ray camera. In the last time digital images are made by computer and printed by a colour printer. The camera "sees" the entire area below the collimator, so that radiations from the whole radioactive region are accepted and processed. So the scintigram is a summarized picture from the organ.

There is a new instrument in the nuclear medicine the **single photon emission computer tomograph**, the so-called SPECT.

The principle of this is very similar to the X-ray computer tomograph, but we use also gamma-radiation isotopes for the imaging. One or two or three scintillation detectors are rotating around the patient and make pictures at certain stemps. From the detected pictures are reconstruated and reorientated by a special computer program and the transversal, sagittal and coronal slices of the organ are made. This method is very useful in the brain examination and in nuclear cardiology, as we will see it later.

There is an other computer tomograph in the nuclear medicine, the **positron emission computer tomograph**, the PET. Positron emitted isotopes, e.g. Fluor 18 is used for the imaging. The annihilation between the positron and the electron produces 511 keV gamma-rays which are detected by PET detectors. The principle of the PET technique is very similar to SPECT examination. The metabolic changes of the tumors, the brain and the myocardium is examinated by these methods.

Radionuclide studies in nuclear medicine

The radionuclide studies are based on a function of an organ or an organ system. An intravenous injection of the isotope is administered to the patients for all examinations, which is uptaked from the blood by the organ function. **So that is an important difference from the X-ray examinations, that the physiological function of the organs is needed for imaging. The examinations are easily performed, needs**

no premedication of the patients, are not associated with any morbidity, have no complication and have only minimal risk. Therefore these are very suitable for screening method.

There are static and dynamic studies, so-called scintigraphy in the nuclear medicine. At the static examinations an optimal time-period after the subject administration is delayed, and several pictures are made from different directions, eg. anterior, posterior, lateral and oblique directions. At the dynamic studies we use computer technic, a picture-serie is stored in the computer from the time of the isotope injection during an optimal time-period of the examined organ function, eg. at the kidney study 25 minutes, at the hepatic study 45 minutes.

There are positive and negativ scintigraphy among the static studies. At the negative scintigraphy pathological decreased activity or lack of the activity is found, which names focal defect. At the positive examinations pathological increased activity is shown, which names hot-spots.

1. Bone scanning

The bone scintigraphy is one of the most important examination in the clinical nuclear medicine. It is a very sensitive study, which becomes positive in the earliest stage of the bone disorders.

The most frequently used agents for this method are the Tc 99m phosphates os diphosphonates. Two or three hours after intravenous injected 600 (six hundred) MBq Tc 99m-labeled phosphate the bone scan can be performed. Bone tissue has high activity for this subject. The effectivity of incorporation depends on the blood supply and on the calcium and phosphorus metabolism of the bone.

Almost every bone lesions can on occasion produce a positive bone scan. The scan may show increased accumulation in primary and secondary tumors, inflammatory diseases (eg. osteomyelitis), arthritides, fractures, metabolic diseaes, Paget′s disease, osteonecrosis, multiple myeloma and so on. These are the indications of this study. The principal value of this method is to find the lesion without defining the etiology of the increased uptake.

Bone scintigraphy is applicated most frequently in the search of metastasis of breast cancer and prostatic tumor. We can see the increased activity of the metastatic lesion, the hot-spot in the bone system half year earlier than X-ray study. The increased bone metabolism already can be shown without changing of the bone structure.

Seldom areas of decreased uptake may be seen in the bone scan, eg. bone cysts and osteonecrosis. Perthes disease is the sterile necrosis of the femur haed in children and a decreased activity can be seen in that area on the bone scan. This examinaton is very useful in the early diagnosis of this disease.

2. Pulmonary scintigraphy

This examination is also very useful technique in nuclear medicine. It can provide an accurate assesment of regional perfusion of the lung. In clinical practice in

adults these studies find the greatest applicability in the diagnosis of pulmonary embolism, but they are also useful in the evaluation of other pulmonary disorders.

Perfusion of the lung can be studied by observing the distribution of intravenously injected radioactive particles. The agents used for this examination are greater in size than human red blood cells, and are therefore trapped in the arteriolar-capillary bed during their first passage through the lung. It is obvious, that if the perfusion from the pulmonary artery circulation to a region of the lung is diminished or absent, the supply of particles to that region will be similarly diminished or absent, and finally it will quantitatively reflect regional perfusion.

A wide variety of particular agents have been used. In our laboratory we use 200 MBq Tc 99m-labeled human serum albumin, so-called macroaggregate albumin with mean particles size of about 30 μm. The particles block only less than 0,1% of precapillary arterioles, and the blockade of this small part of vessels is not permanent. An average pulmonary scanning dose consist of between 200 000 (two hundred thousand) and 1 000 000 (one million) particles. In the lung are over 280 (two hundred eighty) time 10 milliard capillares.

There are four principal indications for radionuclide studies of the lung.

The first is the search for pulmonary embolism in patients with acute symptoms. This is the most common application of lung scanning. An abnormal scan can help in the diagnosis but a normal scan is especially useful since it essentially excludes the presence of pulmonary embolism. It is very important to compare the isotope scan to the chest X-ray picture. If both X-ray and scintigraphy are abnormal in corresponding sites the scan not be used as independent evidence of pulmonary embolism. Almost every abnormality seen on the x-ray will produce a perfusion defect on the scan. But, on the other hand, a defect on the scan couple to a normal X-ray in that area increases the probability of the pulmonary embolism.

The second is the evaluation of regional lung function in patients with lung tumor who are to have lung surgery or radiotherapy. We use the help of computer to this examinations. The residual regional lung function after the surgery can be estimated with this method before the surgery.

The third is the evaluation of regional lung function in asthmatic or obstructive lung diseases.

The fourth is the assesment of regional lung function after the therapy.

3. Thyroid study

It is a very simple method of the investigaton of thyroidal function and structure. I 131 and Tc 99m pertechnetate is concentreted in the thyroid gland are the most frequently used agent for this examination. The Tc 99m image reflects on only the ion trapping function of the thyroid while organification and storage are predominant determinants of the I 131 pictures. In our laboratory twenty minutes after the injection of 37 MBq isotope the scan can be obtained.

The aim of this study is to show the size and the shape of the gland and the cold, warm and hot nodules. A goiter or nodules in or near the thyroid may be easily palpable but their significance may not be clear.

The scan can be valuable adjunct to the diagnosis of extrathyroidal thyroid tissues, eg. aberrant lingual thyroid or functioning metastases in bone of thyroid carcinoma. Upper mediastinal masses may be shown to be retrosternal goiters.

There are diffuse and nodular goiters. The isotope uptake of nodules may be equal, higher and lower than the whole tissue of the thyroid. On the basic of this there are warm, hot and cold nodules. The scan may show multiple nodules even if only one is palpable. It is more difficult to determine the significance of a cold nodule, since the variety of lesions including cysts, benign adenomas, localized thyroiditis, non-toxic nodular goiter or malignancy can all cause nodules with decreased function. There are no particular patterns that absolutely distinguish between benign and malignant nodules.The warm nodules are very rare.

The hot nodules represent thyroid tissue that is functioning automously without control by the pituitary feed-back loop. As the nodule produces increasing amount of thyroid hormone, thyroxine while the remainder of the gland produces less and the euthyreoid state is maintained. This is reflected by decreased isotope uptake in the normal tissue. If the nodule produces an excess of hormone the patient becomes thyrotoxic, TSH levels are completly suppressed the normal tissue becomes inactive and the nodule alone is visualized on the scan.

Liver, kidney and brain scintigraphies also can be performed in our laboratory, but their importance is decreased in the last years by the developement of ulrasound, CT and MRI examinations.

4. Dynamic studies

An important part of the nuclear medicine studies is the dynamic examinations. The principle of that is quite different from all of the other diagnostic methods, eg. X-ray, CT, ultrasound and MRI. With the help of the gamma-camera-connected computer sytem the behaviour of the radioactive agents in the several organs can be followed by outside of the patient from the intravenous injection through the storage to the excretion.

Hepatobiliaric function study

Patients with chronic cholecystic diseases or with obstructive symptomes after cholecystectomy are examined. This liver function is slow enough, so we determine 45 (fourty five) minutes dynamic measurement with 90 (ninety) frames by half minute. The administered 150 (one hundred fifty) MBq isotope, the so-called HIDA is excreted by the hepatic ducts, accumulated in ductus choledochus and goes on into the bowels.
At the evaluation of the study so-called region of interests (ROI) are indicated from the area of peripheral and central parenchyma, ductus choledochus and the bowels, and time-activity curves of this regions are calculated by the computer. The time-activity curve has a T maximum and an excretion half-time. These times have a normal value and when these values are longer, than the normal we can conclude for the certain diseases of the hepatobiliary tract. Eg. when the T maximum is increased, it indicates the damage of peripheral parenchyma. The increased half-time showes the slower

passage through the Vater-papilla because of the obstruction. The indications are on the next slide.
The image and the parameters of damaged function of the hepatobiliary tract and the gall bladder are seen on the next slides.

Camera-renography

With the help of this method we can get an impression from the kidney function.
The detector of the camera is put over the kidneys before the beginning of the measurement. At the moment of intravenously injected 370 (three hundred seventy) MBq Tc 99m DTPA the data collection is started by the computer and that goes during 25 (twenty five) minutes.
We usually begin the study with the examination of renal perfusion. The isotope is given by bolus-technique, which means a very short and rapid injection to the cubital vein. The computer works in so-called frame-mode, when the number and the time of the several frames are determined by us before the examination. For the renal perfusion a fast dynamic is determined, eg. 110 (one hundred ten) frames by 0,5 (o point five) second, while at the camera-renography it is much slower and longer, there are 75 (seventy five) frames and the time of one frame is twenty seconds. This time-period seems to be optimal for the measurment of the kidney function. The time-activity curves are similar to curves in the hepatic study. The increased T maximum means, that the vascular and secretion phase is longer and a parenchymal disorder of the kidney is possible. However when the half-time is longer it shows problems in excretion, eg. nephrolithiasis. We can use the i.v. injection of the diuretic Furosemid during the excretion phase to differentiate between the organical or functional obstruction.
This eaxamination is also very sensitive, which should be performed in the early stage of the kidney disorders.

Out of these two examinations other dynamic measurements from all of the organs can be performed by isotope technique. The perfusion of the brain, the liver, the bone, the peripherial vessels can be made, but these are not so frequently made, than the first two ones.

5. Nuclear cardiology

A very important topic of the nuclear medicine is the nuclear cardiology, which consists of different methods for the measurement of the heart function and perfusion. These studies may be used routinly in clinical cardiology in the menagement of patients with coronary artery disease, acut or chronic myocardial infarctions and other congenital or acquired cardiac diseases.

The gated cardiac blood pool scanning

The gated scan is a technique which provides multiple images of entire heart throughout the cardiac cycle or just end-systole and end-diastole. It represents an

average of many cardiac contractions. It is a technique which permits visualization of the heart in many projections. That is the preferred method for assesment of the ejection fraction and regional wall motion abnormalities.

The technique requires the use of a blood pool agent such as Tc 99m-labeled human serum albumin or red blood cells. These subjects come to equilibrium rapidly within the intravascular space and remain in the heart greater than one hour after the injection. Imaging is performed with a scintillation camera interfaced to a physiological monitor which synchronizes the functioning of the camera to the R wave on the electrocardiogram.

Utilizing the patient′s electrocardiographic signal, the gates may be set to record activity for an interval following the R wave for end-diastole and the T wave for end-systole. 300-600 cardiac cycles are collected and a representative cycle is calculated by the computer from end-diastole through the end-systole to the next end-diastole. 16 pictures are made from this cycle and a time-activity curve is generated, which is really a volume curve.

The ejection fraction is caculated from this curve. The value of this is the stroke volume per the end-diastolic volume in percentage.

The other aspect of this method is to show the akinesis, hypokinesis or paradox wall motion of the left ventricle. This can be seen by continous projection of the 16 frames of the average cardiac cycle on the display, but it can be shown objectively with the so-called parametric pictures, the amplitude-picture and the phase-picture.

The colours on these pictures represent the amplitude and the phase of the wall motion. The hypokinetic area or the paradox wall motion are appeared with other colours.

The main indication of this study is to determine the ejection fraction and the wall motion abnormalities in patients with acute myocardial infarct and further control examinations during the treatment and the rehabilitation.

Myocardial perfusion imaging

The next topic of the nuclear cardiology which I would like to talk about is the myocardial perfusion study in rest and is stress/rest situation. Coronary arteriography has been used many years to locate and estimate the extent of obstructive coronary artery disease, but this method is invasive and dangerous. A critical stenosis could be defined as one which leads to myocardial ischemia, so many out come of such condition can be avoided with prior knowledge about the stenotic lesions. Several scintigraphic methods have been developed for the determination of regional myocardial blood flow and when one of these is used in conjunction with stress, regional reduction in radioactivity provides physiological evidence of the significance of a given coronary stenosis.

The method have been described with an intravenous injection of a diffusible extractible actively concentrated substance such as monovalent cation Tl 201(two hundred one) chloride. This kation is compatible with the potassium-content of myocardium. It is actively concentrated in the myocardium by the function of the sodium-potassium ATP-ase sodium pump and in the relation of the myocardial

perfusion. In the presence of significant stenosis or obstruction a decreased activity of the myocardium has been shown. A few years ago a new subject was developed for this examination, which advantage is, that it can be labeled by Tc 99m, namely the MIBI (methoxy-isobutil-isonitrile) and the tetrofosmin. The main different from the Tl 201 is the absent of the redistribution, the stress and rest examinations must performe by two injection of MIBI both in one-day or two-days protocol. They are the most commonly used agents for this study. They are trapped in the mitochondria of the myocytes and it is related of the blood supply by the coronary arteries. The supplied areas of the sveral branches are seen on the next slide.
Short axis coronal and lon axis transversal and sagittal slices are made from the left vintricle myocardium.
The indication of rest study is to show the size and the localization of the scar in myocardial infarction.The rest examinations are indicated also in rest angina.
The indication of stress/rest study is the obstructive coronary diseases, before and after the catheterization, PTCA and by-pass surgery.
On the first day we make the examination in stress conditions. Physical or pharmacological stress (e.g. dipyridamol) is applied. On the next day the study is repeated in rest condition. The stress/rest mismatch is the sign of the transient ischaemy. In the presence of significant stenosis of the coronary arteries a decreased activity of the myocardium is found on the pictures in stress. In the rest the distribution of the isotope is followed by the improvement of the perfusion and the decreased activity is disappeared.
The stress and the rest myocardial slices are compared on the SPECT image.
Of course, the uptake of this agent by infarcted or scarred myocardium is also extermly reduced both in stress and rest, too. The presence of myocardial infarction is verificated by this persistent perfusion defect.

6. ***Brain perfusion study***

This examination is investigated by 500 MBq 99mTc-HM-PAO (hexamethylen-propylenamin-oxym), which is a lypophil agent, it is trapped in the cortex and in the basal ganglia. This is a SPECT study, using of the double-head SPECT is very advantageous in the shorter examination time period. The distribution of the subject in the brain is depend on the blood supply in the carotis system.
In normal cases the the activity is homogenous, we can not see any hypoperfusion in the different parts of the cortex
The perfusion changes of the cortex are very different in the several neurogical illnesses. There are other changes in the brain perfusion, e.g. the stroke, the Pick disease, the epilepsy, the internal carotis occlusion, the migraine, the suspect transient ischaemic attack (TIA), when we can see hypoperfusion or hyperperfusion in the different parts of the brain cortex.

7.Nuclear oncology

It is also consist of some different methods to investigate the properties, the size, the localization and the matastases of several tumours.

Sentinel lymph node scintigraphy

The basic principle of this examination is to find the sentinel node of the tumours and to investigate its histological patterns after the excision. When the histology of the sentinel lymph node is not malignant, the patient needs no to total excision of the lymph nodes and his/her life quality in the future would be more better than after the total exstirpation.

Neuroendocrine receptor scintigraphy

A specific method for the investigation of the neuroendocrine tumours is the 131-iodine-methaiodobenzyl-guanidine (MIBG) scintigraphy. This subject labels to the neuroendocrine receptors.
In the case of pheochromocytoma and neuroblastoma which contains neuroendocrine receptors we can find the tumour and the metastases by 111-indium-MIBG in the whole body picture and by SPECT imaging, too.

Somatostatin receptor scintigraphy

This is also a specific examination to show that malignancies, which contains somatostatin receptors on their surface, e.g. carcinoid tumours, small cell lung cancers and medullary thyroid cancer. The used subject is the octreotide or depreotide which are labeled by 111-indium, or 99m-Tc.
These new receptor studies together with the PET metabolic studies are very useful in the differential diagnosis of the different tumours in oncology.

That was the very short summary of the basis of the clinical nuclear medicine. I hope, that it was clear and you understood the importance of these methods in the clinical diagnosis.

About the FUTURE…

Nowadays one PET and three PET/CT equipments are working in Hungary one in Debrecen and twoo in Budapest. It means very few eaxmination for 10 million people. The University Centers are working on this project to get more PET-CT. These examinations are very useful in the oncology, e.g. to investigate the metabolic patterns of the tumours by labelled glucose, methionin, free fatty acids, and so on.

The other possibility to make better the diagnostic is the fusion imaging, when the pictures of the different methods are fusioned on the picture. So we can see the body structure by CT or MRI and the functional patterns by SPECT or PET are fusioned on the same picture. There is an equipment for this purpose, a SPECT/CT in Pécs, in our Institute, which is the first SPECT/CT in Hungary. These fusion imaging can give very good results in the diagnostics.