Alzheimer’s Disease (AD) is described as a degenerative disease of the central nervous system characterized by a noticeable cognitive decline defined by a loss of memory and learning ability, together with a reduced ability to perform basic activities of daily living. In the brain of an AD patients is the dramatic decrease in cholinergic innervation in the cortex and hippocampus due to the loss of neurons in the basal forebrain. The above findings led to the development of the cholinergic hypothesis, which proposes that the cognitive loss associated with AD is related to decreased cortical cholinergic neurotransmission. In brain of Alzheimer’s patient’s one ascertained presence of neuritic plaques containing the beta-amyloid peptide and protein tau. Biochemical and genetics studies implicated a central role for beta-amyloid in the pathological cascade of events in AD.

The most therapeutic strategies in AD have been directed to two main targets: the beta-amyloid peptide and the cholinergic neurotransmission. The first approach is to act on the amyloid precursor protein (APP) processing. The second main approach is to slow of decline of neuronal degeneration or increasing cholinergic transmission.

Diagnosis of AD is very difficult and to date no specific diagnostic tests of the disease are available. Intellectual function testing to determine the degree of cognitive status during routine medical examination is a useful supplementary method of diagnosing dementia. The permissible result, come down from radiopharmacy, which is an integral part of a nuclear medicine. A radiopharmaceutical may be defined as a pharmaceutical substance containing radioactive atoms. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are capable of mapping the distribution of radionuclides in three dimensions, producing maps of brain biochemical and physiological processes. The techniques are reasonably sensitive and specific in differentiating AD from other dementias.

**Keywords**: Alzheimer’s disease, Diagnostic, PET, SPECT

Alzheimer's disease accounts for 50% of dementia-type syndrome, characterized by organic disorders related to cognitive functions. It is chronic neurodegenerative pathology of the central nervous system like Parkinson's and Huntington's diseases, exacerbating in the course of time.

The symptoms of Alzheimer's disease were first described by Alois Alzheimer in 1907. It is characterized by gradual and progressive worsening of daily activities, behavioral and cognitive functions. Approximately 8 years pass from the onset of disease to death. Initially, a subtle decline in concentration and memory is observed, the patient has to put more effort in order to achieve the aim. These symptoms are non specific and can also imitate stress, exhaustion or appear as normal senile processes. That is why they are often belittled. In next stages of the disease symptoms include short-term memory loss and impaired ability to perform instrumental activities of daily living. Subsequently, blackouts appear, the patient remembers issues from the past, but the person does not recollect facts from yesterday, loses orientation related to time and environment, and is not able to make up straightforward decisions unaided. In the advanced stage the patient has difficulties with daily activities and does not control physiological functions. In 5 years time the patient becomes dependent on his/her caregivers. Consciousness disorders and frequent mood fluctuations such as apathy or agitation can be detected.

Alzheimer's disease is diagnosed in patients after the age of 65. In the developed countries the percentage of persons with Alzheimer's disease between 65 and 70 years of age amounts to 2.5%, approaching 25-30% in persons over the age of 85. Globally, approximately 20 million persons suffer from this pathology. It is a serious social and economic problem, including direct costs of the treatment and in addition costs 24 hr care in nursing.
Pathology of Alzheimer's disease

Currently, causes of the disease are not fully recognized. In approximately 40% of patients the congenital background of the disease is identified, for which mutations in 1, 14, 19 and 21 chromosome in genes are responsible. It is assumed that some protein metabolism disorders in the central nervous system (CNS) initiate the disease leading to the formation of toxic products\(^6\). Taking into consideration morphological changes in Alzheimer's disease, senile plaques so called amyloid deposits are detected. They appear in the intercellular compartments, especially in the hippocampus and cerebral cortex, composed of non-soluble beta-amyloid (A\(\beta\)), distrophic neurons, microglia and astroglia\(^6\). Beta-amyloid is formed on the basis of the amyloid precursor protein (APP). This protein is decomposed by alpha-secretase or beta- and gamma-secretases. In this first case APPs (soluble protein) is formed which has neurotrophic properties, especially neuroprotective. Transformation of APP by beta- and gamma-secretases leads to beta-amyloid formation which in soluble form does not reveal neurotoxic properties. Presumably mutation in one gene causes formation of fibrillary beta-amyloid which in this form destroys structural proteins of neurons. It leads to significant neuronal conduction impairment. It should be emphasized that amyloid plaques appear in the elderly, but in a significantly lower amount as compared with patients with Alzheimer's disease. Protein deposits inside neurons, called neuronal fibrillary degeneration or neurofibrillary tangles are morphological lesions characteristic for Alzheimer's disease. They are composed of two spliced threads of highly phosphorylated tau protein which normally stabilizes nerve cells. Neurofibrillary tangle condensation is tightly associated with the stage of the disease. A hypothesis exists that senile plaques which appear earlier in Alzheimer's disease in comparison with tau protein are prerequisite factors for neurofibrillary tangle formation\(^6\).

In autopsy reports a significant decrease in the number of cholinergic neurons has been observed in the brains of patients with Alzheimer's disease, especially in the neocortex and hippocampus. Since acetylcholine (ACh) is a neurotransmitter associated with memory and learning, on the basis of these data a cholinergic theory of Alzheimer's disease has been formulated\(^7,8\). As a result of the decreased acetylcholinesterase activity, the level of acetylcholine declines which leads to the decreased cholinergic neurotransmission. A decline in cholinergic neurotransmission in the regions of brain responsible for higher intellectual processes is a cause of cognitive and behavioral disorders in patients with Alzheimer's disease. In this pathology dopamine, serotonin and gamma-amino butyric acid (GABA) neurotransmission was impaired.

Mechanism of acetylcholine formation

Acetylcholine (ACh) is formed from choline and acetyl-CoA under the influence of acetylcholinesterase\(^2\). It is stored in the synaptic follicles in the presynaptic part of neuron. The secretion of neurotransmitter to the neuronal gap junction is mediated via action potential and following opening of the calcium channel. Released ACh is bound to the postsynaptic receptor, causing an increase in the permeability to sodium ions. In the neuronal gap junction free acetylcholine is decomposed into choline and acetic acid by cholinesterase. Released choline takes part in the synthesis of acetylcholine. Acetylcholine stimulates pre- and postsynaptic muscarinic and nicotinic receptors\(^9\).

In the central nervous system there are two types of cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). They are homologous in 65% cases, despite the fact that they differ in amino acid sequence and they are coded in chromosomes by various genes. AChE is located mainly in the neurons, and BuChE in the glia. Both enzymes hydrolyzes acetylcholine with the speed of 10 000 molecules per second. Acetylcholinesterase hydrolyzes acetylcholine selectively, and butyrylcholinesterase can hydrolyze other particles, including neuroactive peptides. It is a consequence of differences in the structure of both enzymes. These enzymes have active groove 20 Å deep and 4Å wide, in which acetylcholine enters. It binds to enzymes in two locations: catalytic, located close to the groove base and anionic, located at the “gorge” of enzymes. In the cationic location, which influences the speed of bond between acetylcholine and the enzyme, there are two molecules of phenylalanine (Phe295) and (Phe297), whose aromatic residues approach the inside of the
channel. Catalytic point is responsible for the substrate affinity for the enzyme, including among others triptophane (Trp84), serine (Ser122), glycine (Gly118) and histidine (His 460). An amino acid sequence at the “gorge” of the enzyme constitutes a significant difference between acetylcholinesterase and butyrylcholinesterase. BChE instead of phenylalanine has two smaller amino acids: valine and leucine. The role of butyrylcholinesterase is not fully explained. However, due to the advancements of molecular biology it was assessed that it played a vital role in soluble beta-amyloid transformation into its toxic, non-soluble form.

In the brain of healthy person AChE is responsible for 80% of cholinesterase activity, and BChE for the remaining 20%. In case of advanced Alzheimer's disease acetylcholinesterase activity can decrease to 55% of the normal level, and activity of butyrylcholinesterase can increase even several times. A ratio of these enzymes can be a determinant of the disease progression.

Trends in Alzheimer's disease therapy

Searching for causally-acting medications—Since the cause of the disease is not fully known, medications have not been found yet, which can treat patients with Alzheimer's disease completely. Huge hopes are associated with search for medications inhibiting formation of toxic beta-amyloid or alleviating negative side effects. Presumably compounds increasing neuroprotective metabolism of the precursor protein (APP) with the participation of alfa-secretase can play such a role. There are researches on selective agonists of muscarinic receptors (M1), which increase the formation of APP, decreasing at the same time decomposition of APP by beta-secretase. Inhibitors of beta and gamma-secretases can also play an advantageous role, which also inhibit the toxic beta-amyloid formation. Synthesis of drugs showing such action, characterized, at the same time, by good pharmacokinetic properties is a matter of time.

As mentioned above, beta-amyloid in a soluble form, contrary to the fibrous form does not show neurotoxic properties. Substances inhibiting its aggregation could play a significant role in the causal treatment of AD. In vitro examination Congo red can perform a useful function. Experiments are being conducted consisting in administration of genetically modified cells to the brain, which could be a prophylaxis of senile plaque formation and neurofibrillary degeneration.

Perception of a mechanism of the pathologic protein metabolism stimulates the scientists to search for vaccination which could mobilize the organism to get rid of toxic deposits from the intercellular compartment.

Causal treatment of Alzheimer's disease—Causal treatment is at present the only, moderately effective therapy used in Alzheimer's disease. Drugs which in indirect or direct way increase the level of acetylcholine in the central nervous system, play a crucial role. An increase in the level of this neurotransmitter has a advantageous influence on the amelioration of memory and cognitive functions, which aids the patients with self-reliant existence.

Precursors of acetylcholine—Initially researchers tried to augment the level of ACh in the central nervous system acetylcholine precursors such as lecithin or choline. These substances have an advantageous influence on the cell membrane of neurons, however current studies do not confirm their efficacy in the treatment of Alzheimer's disease.

Inhibitors of acetylcholinesterase—The best effects in the causal treatment of Alzheimer's disease can be achieved with the use of acetylcholinesterase inhibitors. They delay intra-synaptic degradation of acetylcholine by acetylcholinesterase which leads to the increased accessibility of ACh in the synaptic gap junction. It causes an increase in postsynaptic stimulation of muscarinic receptors, ameliorating at the same time cholinergic neurotransmission. They act especially advantageously in the initial stages of the disease. Currently registered inhibitors of AChE differ in the structure, mechanism of action, and also in selectivity to the given regions of the brain and selectivity towards AChE and BchE. Taking into consideration time of action and the way of binding to the enzyme, inhibitors are divided into reversible (they block the enzyme for a short time), irreversible (long time of action, they create long-lasting complexes with acetylcholinesterase) and quasi-reversible (reversible, but they show a very long time of enzyme blockage). Taking into consideration the structure, among inhibitors we distinguish basic derivatives of carbamates, acridine, benzylpiperidine and phosphoorganic esters. All inhibitors show action in the intersynaptic part of cholinergic neurons. To examine interactions between tacrine (in
protonic form) and the enzyme, we have found 4 bond types:

1. hydrogen bonds between proteins and the molecule structure surrounded by water molecules
2. \( \pi-\pi \) interactions of aromatic rings, mainly between W84 and F330
3. interaction between nitrogen cation and \( \pi \) bond of the aromatic systems
4. hydrophobic contact of the inhibitor and protein not connected by hydrogen bond

**First generation of AChE inhibitors:**

Physostigmine — pyrrolidine and indoline alkaloid, including carbamate group. This compound is a quasi-irreversible inhibitor, which was first clinically tested in Alzheimer's disease. In a significant way it enhances memory in patients, but at the same time it increases the level of anxiety and irritation (so called physostigmine syndrome). It also affects the peripheral cholinergic system, causing nausea, vomiting and diarrhea. Side effects of physostigmine result from its short half-time of an radioisotope (T\( \frac{1}{2} \)=30min)

Tacrine (Cognex) — is an aminoacridine derivative (Fig. 1). It is a reversible inhibitor, registered in 1993 by FDA in the USA as a first drug in Alzheimer's disease. It shows higher affinity for butrylycholinesterase as compared with acetylcholinesterase. Its half-time is 1.5-3.5 hr. Initial publications reported on the improvement in life conditions in patients and inhibiting symptoms. Subsequently, it was revealed that tacrine was hepatotoxic and impair the cardiovascular system. In patients an elevated level of alanine aminotransferase was detected (those enzyme transfered chemical groups between compounds). After a cessation of treatment, the level of transferases returned to normal levels and patients began this therapy once again, because it was among very few medications to treat symptoms of Alzheimer's disease. Tacrine has an influence on the cholinergic system causing nausea, vomiting, abdominal pain and diarrhea. In spite of the symptoms, it is used in 25-30,000 persons all over the world.

**Second generation of AChE inhibitors**

The second generation of acetylcholinesterase inhibitors encompasses registered inhibitors (donepezil, rivastigmine, galantamine) and numerous drugs, clinically tested in different stages, of a potential activity of esterases.

Donepezil (Aricept) — N-benzylpiperidine and indane derivative is a reversible and non-competitive AChE inhibitor (Fig. 2). During the blockage of the enzyme a complex is formed, in which N-benzylpiperidine group reacts with anionic center of the enzyme. Currently, it is the most frequent drug in the medium stage of Alzheimer's disease. It is characterized by long half-time (T\( \frac{1}{2} \)=70 hr) and approximately 1250 higher affinity for acetylcholinesterase as compared with butrylycholinesterase. It shows high affinity to the brain and significantly stimulates the cholinergic system. Donepezil decreases the level of anxiety and does not lead to the excessive stimulation of the patient. Patients, which take donepezil are less irritated, in better mood and less frequently depressed. Side effects can occur when this drug is administered in high doses or after a long time of usage. Contrary to tacrine no cases of hepatotoxicity were found.

There are also promising compounds, in which indane (Fig. 2) group is replaced by various heterocyclic groups e.g. bioisosteric derivatives of...
N-benzylpiperidinebenzisoksazole showing higher activity and selectivity as compared with donezepil and are efficient in animal cognitive models. T-82 (Fig. 2) compound shows two-way action: it inhibits AChE and is antagonistic towards 5-HT₃ receptors. Currently, it is under clinical studies.

Rivastigmine (Ekselon) — quasi- irreversible inhibitor is a derivative of carbamate (Fig. 3). Half-time of this compound is $T_{1/2}=2$ hr, however it can block the enzyme for 8-10 hr. Rivastigmine was registered in Europe in 1998, and in the United States in 2000. This drug shows similar action as physostigmine e.g. as a result of carbamoylation of serine it causes the blockage of the active center of acetylcholinesterase. Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase. It reveals selective action both on the cortex and hippocampus. That is why it does not cause significant side effects. This medication is not hepatotoxic, because it is metabolized only by cholinesterase. It significantly decreases mood disorders, improves cognitive functions and abilities to perform daily activities. As a result of the modification ofphysostigmine new derivatives of carbamates have been obtained. Fenserine, which is formed as a result of replacing methyl group with phenyl ring in physostigmine, is in the first phase of clinical studies. It is characterized by high activity, long time of action and high selectivity to acetylcholinesterase. It significantly enhances memory. Some derivatives of fenserine for example cymserine or N-phenylethylencymserine selectively inhibit butyrylcholinesterase. Taking into consideration the fact that the level of this enzyme increases during Alzheimer's disease and its role during formation of toxic beta-amyloid, selective inhibitors of butyrylcholinesterase can play a vital role in the therapy of this disease in the future.

Examining physostigmine analogs we have found out that the location of the carbamate group in phenyl ring has a crucial effect on their activity as acetylcholinesterase inhibitors. Derivatives, in which carbamate group is in the location 6, show 60-550 times higher action as compared with compounds, in which this group is located in the position 7 or 18 (ref. 16).

Ro 46-5934 compound is a selective inhibitor of AChE and shows an antagonistic action towards muscarinic receptors (M2). It significantly increases the level of ACh. Other derivative- CHF2819 increases the level of Ach and serotonin in hippocampus, which can be useful for the treatment of depression, frequently diagnosed in Alzheimer's disease; Both derivatives are in the course of clinical studies.

Galantamine (Reminyl) — is a phenanthrene alkaloid, from the plants of Amaryilliadaceae (Fig. 4). It’s half-time is 6 hr, while one of this metabolite inhibits cholinesterase. Galantamine shows two-way action – reversible and competitive blockage of acetylcholinesterase (mainly) and modulation of the nicotinic receptor response to acetylcholine. Apart from the increase of acetylcholine, galantamine augments the level of glutamic acid and gamma-amino butyric acid in the central nervous system. The use of galantamine ameliorates cognitive functions and delays impairment of various daily activities. Ester analogs of galantamine – symbols P11012 and P11149 are pro-drugs, which in vivo are rapidly hydrolized to 6-demethylgalantamine. This compound is tenfold more active and sixfold more selective as compared with galantamine.
In China research was conducted on (-)-huperzine A, alkaloid isolated from *Huperzia serrata*. This research showed high efficacy of this alkaloid as a selective inhibitor of AChE. It is characterized by a long time of action and very low toxicity, moreover it shows neuroprotective properties towards neurons of the hippocampus and cortex. It significantly improves memory. It should be mentioned that this alkaloid has been used for ages in Chinese medicine for the treatment of diseases of the central nervous system.

Metriphonat is an ester of phosphonic acid, which is irreversibly blocked by acetylcholinesterase and butyrylcholinesterase. It represents the group of non-active prodrugs, which via non-enzymatic hydrolysis is transformed into the active metabolite- dichlorvos (DDVP). This compound blocks the ester center of the enzyme via phosphorylation of serine in the catalytic location of acetylcholinesterase. Currently, metriphonate is being evaluated.

Searching for new inhibitors focuses on the augmentation of known structures by duplication or combination of active fragments of various compounds in one molecule. The obtained dimers composing of key fragments of tacrine, huperzine A or galantamine, united by maleylene chains of adequate length, show activity towards both locations which bind acetylcholinesterases. Bis-tacrine is an example of such substance with approximately 150-fold higher activity than tacrine, moreover, it is very efficient in animal cognitive models and shows protective action in oxidative stress.

Hupurzine X and Y (Fig. 5) are compounds formed as combination of 4-aminochinoline derived from tacrine with bicyclic carbon ring (-)-huperzine A. Since tacrine and hupurzine A are located very near and partly overlap, the obtained derivatives of hupurzine reveal higher affinity for binding to active locations of acetylcholinesterase. The obtained compounds are promising, novel reversible AChE inhibitors with good pharmakokinetics and higher activity in comparison with tacrine, (-) huperzine A and donepezil.

The drug described as TV3326 also reacts with two active locations. It includes phenyl group of N-ethyl-N-methylcarbamate derived from rivastigmine, combined with rosagiline fragment (N-propargyl-(1R)-aminoindanone). Rosagiline is a selective MAO-B inhibitor. This formed hybride shows affinity for acetylcholinesterase with simultaneous action on monoamine oxidases (MAO-A, MAO-B). It also reveals neuroprotective, antidepressant properties and improves cognitive functions.

Compounds improving the secretion of acetylcholine from the presynaptic nerve endings:

**Blockers of potassium channels**

Such drugs cause an increase in the level of acetylcholine. The first clinically tested compound was linopiridine (DuP 996) which was not very efficient in patients with Alzheimer's disease, probably due to short half-time of action and weak penetration through blood-brain barrier. Structural modifications consisting in the insertion of tricyclic anthranone instead of 2-indoline and introduction of fluorine in the ortho- position to nitrogen atom of pyridylmethyl group, lead to more lipophil compound described as DMP 543, which *in vivo* reveals high activity and is currently being investigated.

Besipiridine (HP 749) is a more lipophil derivative of 4-aminopiridine. Recent researches prove that this drug better reacts with sodium channel than potassium channel. Currently conducted research on besipiridine proves its cholinomimetic and adrenergic properties. DMP 543 and besipiridine increase also the level of dopamine and aspartic acid in the central nervous system.

**Agonists of nicotinic receptor**

In Alzheimer's disease a decrease in the number of neuronal nicotinic receptors in the cortex and hippocampus can be found. The activation of these receptors leads to the secretion of acetylcholine, dopamine and noradrenaline- neurotransmitters associated with learning and memory. Nicotine, which stimulates all known subtypes of nicotinic
receptors, ameliorates memory. Unfortunately, it causes a lot of side effects such as anxiety, mood fluctuation, nausea, vomiting. ABT-418 and GTS-21 derivatives, which improve memory and concentration with better neuroprotective properties and lower toxicity as compared with nicotine, are formed on the basis of modification of pyridine or pyrolidine ring in nicotine.

Agonists of muscarinic receptors

Biological effect of the agonists of muscarinic receptors is the same as acetylcholinesterase inhibitors e.g. an increased level of acetylcholine in the central nervous system. They can be more efficient than inhibitors, acting independently of the degree of presynaptic cholinergic neuronal degeneration in the cortex and hippocampus. In Alzheimer's disease the number of presynaptic M2 receptors, secreting acetylcholine, is decreased, whereas postsynaptic M1 receptor is not impaired. M1 receptors play a significant role in memory process, that is why scientists search for these receptor agonists.

Presumably, the aforementioned agonists of M1 muscarinic receptor accelerate APP transformation into its soluble form (APPs), inhibiting at the same time formation of toxic beta-amyloid. These facts explain the great number of compounds in various phases of clinical trials.

The first generation of the agonists of muscarinic receptors (arecoline, pilocarpine) were characterized by low bioavailability, short time of action and side effects of cholinergic type. The second generation compounds are more selective with better pharmacokinetic properties. Unfortunately, III phase of clinical trials proves that many drugs, useful in Alzheimer's disease, reveal many side effects, which eliminate them from further investigation. Milameline and subcomeline are among such medications.

Talsaclidine and the compound described as YM-796 are selective agonists of M1 receptor and show also nootropic properties.

Talsaclidine is an ether derivative of chinuclidine, characterized by good pharmacokinetics without side effects.

YM-796 was formed on the basis of the active fragments of muscarine and arecoline. It significantly improves memory and learning abilities. Both compounds are under clinical trials.

Adjuvant treatment

In the adjuvant treatment of Alzheimer's disease medications are used, which affect the processes in the central nervous system, ameliorating to some extent patients' functions. These substances act as receptors or by other mechanisms. They help mainly with treatment of dementia. Memantine and selegiline (Fig. 6) act via receptors, activating adequate neurotransmitters.

Memantine — It is the only registered drug, acting via cholinergic system. Its mechanism of action is based on the activation of ionotropic glutaminergic receptor NMDA (N-methyl-D-aspartate), which improves glutaminergic neurotransmission. Memantine is used also in Parkinson's disease and in numerous syndromes.

Selegiline (Jumex) — It is a MAO inhibitor, which affecting the catecholamine system, increases dopamine concentration in the central nervous system. Thanks to it, it improves cognitive processes and influences advantageously behavioral functions in patients.

Selegiline (Deprenyl) - It protects cerebral lipids from oxidative stress. It significantly delays the loss of cognitive functions in patients with moderate dementia.

Vitamin E, C — their role is to neutralize free radicals. Further research is needed to confirm their advantageous influence on Alzheimer's disease.

Egb-761 (Ginko biloba extract) — it acts as an antioxidant and inhibits peroxidation of lipids. To
small extent but efficiently, it delays the progression of dementia\textsuperscript{4,20}.

Anti-inflammatory drugs — epidemiological studies prove that the use of non-steroid anti-inflammatory drugs cause the decrease in inflammatory processes in the brain and lowers the level of beta-amyloid\textsuperscript{20}.

Piracetam (Nootropil) — a nootropic drug (Fig. 6), which improves neuronal metabolism in the brain and protects the central nervous system from various harmful factors. Clinical trials confirm an advantageous influence of Nootropil on the enhancement of patients memory and concentration\textsuperscript{13,20}.

**Diagnostics of Alzheimer's disease**

Due to the characteristic morphological features in patients with Alzheimer's disease, the only and certain method of diagnosis, not so long ago, was the detection of specific lesions in the post-mortem examination.

Practically, for a proper diagnosis, apart from the laboratory tests, medical history of the patient and data taken from his/her close caregivers were essential. Moreover, it should be stated whether in the patient characteristic clinical features of dementia-type syndrome exist (including Alzheimer's disease).

Initially, at least two disorders of cognitive functions should be found. The diagnosis can be established when these symptoms maintain for at least 6 months. If possible, also other disorders such as depression or endogenous psychosis should be excluded in order to obtain moderately clear image of the disease. Collected information should be confirmed on the basis of standardized tests assessing cognitive functions. Mini Mental State Examination (MMSE) and drawing of the clock are among them. The former option assesse s the basic cognitive activity e.g. orientation related to time and place, remembering, concentration, calling, reading, writing, following complex orders and constructive praxis. For a proper solution of this test the patient can obtain maximally 30 points. The patients with results below 24 points are suspected of Alzheimer's disease and are qualified for further investigation. On the other hand, a test of drawing the clock assesses visual-three-dimensional abilities, constructive praxis, abstractive thinking and executive functions. This investigation does not guarantee, however, certain diagnosis, and its positive result does not exclude that the examined patient is healthy.

The subsequent phase of clinical trials is to determine the degree of functioning in the society. The Instrumental Activities of Daily Living (ADL) scale enables this examination. It describes the abilities to perform daily activities.

Instrumental Activities of Daily Living (IADL) scale depicts patient’s abilities to undertake tasks associated with work, journey, keeping a promise etc. In advanced and intermediate disease daily activities impairment can be detected, according to the scale depicting the ability to perform properly daily activities, e.g. washing, dressing or eating\textsuperscript{31}.

The above mentioned tests and examinations feature the patient's health status. Current diagnostic methods permit identification of the brain dysfunction, neuronal degeneration degree and topography. Imaging diagnostics with the use of radiopharmaceuticals is a matter of great importance for detection of Alzheimer's disease\textsuperscript{22}.

At present, they are the only non-invasive and reliable tests imaging the brain degeneration and worsening of the disease. They permit with great probability detection of pathology before first clinical symptoms appear. In this case early diagnosis is associated with a delayed progress of the disease, and at the same time with the amelioration of the quality of life.

Modern methods of searching for drugs and diagnostic pharmaceuticals use receptor, enzymatic mechanisms or protein transporters of endogenous ligands. Fluorine-labeled benzodiazepine derivative-[\textsuperscript{11}C]flumazenile is an example of receptor mechanism.

A rapid development of tomography has been noted in last two decades\textsuperscript{25, 26}. Single photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MR) are used for non-invasive imaging of the brain. Nuclear magnetic resonance (NMR) was introduced at the turn of the seventies and eighties of the previous century, but research on nuclear magnetic resonance had been conducted much earlier. In 1938 Isidor I. Rabi from the Columbia University carried out pioneering research on nuclear magnetic resonance, for which he was awarded with the Nobel Prize in 1944. In 1946, working separately, physicists- Felix Bloch from the Stanford University and Edward Pruccell
from the Massachusetts Institute of Technology discovered the phenomenon of NMR in solid bodies, for which they were also awarded with the Nobel Prize in 1952. Raymond V. Damadian suggested implementation of magnetic resonance in medical diagnostics, publishing in 1971 “Detection of cancer using nuclear magnetic resonance”. He also built the first NMR tomograph. Since that time this equipment has been routinely used in medical diagnostics. NMR is based on the absorption of electromagnetic radiation of the frequency of 10-360 mHz (radio frequency) by atom nuclei. Only nuclei with magnetic moment can resonate after placement in the strong magnetic field. SPECT differs from PET in the type of given radioactive isotope and data registered. In these methods two-dimensional distribution of the given isotope is noted. These both methods permit identification of various brain dysfunctions and neuronal degeneration degree and topography. In Alzheimer’s disease to a certain extent, they can differentiate these patients from those with other pathologies characterized by similar clinical picture.

Radiopharmaceuticals are the compounds showing selective affinity for the given organs, therefore they are used in diagnostics. Such pharmaceuticals are represented by $^{99m}$Tc with phosphonic acid e.g. medronic acid. They accumulate in the bones and, therefore, they are used among other things for early detection of neoplastic lesions in the bone tissue.

SPECT permits the detection of degeneration before visible changes within the limbic system occur and clinical symptoms are manifested in the patient. Even in the early phase of the disease we can detect, with the use of this method, e.g. insufficient blood flow in the temporal and frontal lobes. In SPECT tomography to diagnose the central nervous system only such pharmaceuticals are used, which cross the blood-brain barrier. To image the local blood flow disorders in Alzheimer’s disease, n-isopropyl-$^{123}$I-iodoamphetamine constitutes a source of radiation. The substances are labeled with radioactive technetium ($^{99m}$Tc), which is obtained from the molybdenum reactor. Hexamethylpropylamine oxide ($^{99m}$Tc-HMPAQ) and ethyl ester of $^{99m}$Tc-ethylidicysteine ($^{99m}$Tc-ECD) and $^{57}$Co derivatives represent such compounds.

PET is also a very sensitive, non-invasive diagnostic tool. Radiopharmaceuticals used in this method emit positrons. Positrons due to very short life time unite with electrons of the surrounding matter. They emit at the same time photons which are carriers of message to the organs (same as SPECT). The value of PET is also that this method permits not only description of the location affected with the disease, but also enables observation of the translocation of the labeled substance in time. It permits observation of various metabolic processes depending on the ligand used containing radionuclide. Radionuclides emitting positrons belong to the elements especially important for metabolic processes in organism (e.g. $^{11}$C, $^{15}$O, $^{18}$F, $^{10}$N). Physiological substances are labeled with these elements, and subsequently there metabolites are examined e.g. metabolites labeled with glucose are good indicators of the intensity of biochemical processes in organs.

On the basis of disorders of glucose metabolism and excessive glycation of proteins Alzheimer's disease can be detected before the onset of atrophic changes and first clinical symptoms which are ignored very often. Currently, 2-[$^{18}$F]fluoro-2-deoxy-D-glucose is at the stage of clinical research. There are advanced research on the use of acetylcholinesterase inhibitors such as donepezil or tacrine in PET. In order to use them for monitoring the course of the disease, these compounds should contain radioactive atom. Modification in the structure of donepezil consists in the replacement of carbon in the position 6 for radioactive isotope ($^{11}$C). In case of tacrine in the position 7, $^{18}$F or $^{123}$I were introduced. $^{11}$C-methyltacrine was also obtained.

Positron emission tomography is also used for the assessment of donepezil activity in the brain. To achieve this aim, studies with acetate and propionate of N-$^{11}$C-methylpiperidine have been conducted.

Summary

The prevailing use of the aforementioned neuroimaging techniques is limited, above all, by the access to the diagnostic centers and high costs of the equipment, especially generators with short half-period of radioisotopes.
Nevertheless, it seems that scintigraphic methods can play a significant role in the early detection of neurodegenerative diseases including Alzheimer’s disease. Further amelioration of scintigraphic methods will consist in the detection of new radiopharmaceuticals, better detection of photons (e.g. by means of lutetium oxyorthosilicate - LSO) and in the progress of reconstruction of the obtained three-dimensional images and data analysis.

Hopes for the efficacious treatment of Alzheimer’s disease are pinned on medications with two-way action and gene therapy.

References
34. Akula M & Longford C, Synthesis of 9-amino-7-[18F]fluoro-1,2,3,4-tetrahydroacridine: A potential PET agent to map acetylcholinesterase in Alzheimer patients, Second Annual Research Day University of Tennessee Medical Center in Knoxville TN, 42 (1998) 539.

