

New Therapy 's Prespective For Alzheimer's Disease

Chiara Spera

School of Pharmacy, University of Salerno, Italy

e-mail: sperachiara@alice.it

Summary

“Imagine yours brain a san illuminate house. Now imagine that somebody turn off the light; this is what makes Alzheimer. Turn off the light in a room and then in the others and ideas, emotions and memory weaken and stop finally. Unfortunately, as knows sick's parents, there isn't a way to avoid turn off the lights, at least for now.¹”

The Alzheimer's disease is a neurodegenerative pathology, as Parkinson's disease, Amiotrophic Lateral Sclerosis and Huntington's Chorea. Common peculiarities of these pathologies are progressive neuronal loss in specific brain areas. There are very shed pathologies typical of senile age, can, but, rise up in juvenile age too. The therapeutic treatment of this diseases is purely symptomatic and not change the course or progression of the disease. Alzheimer's disease in these years have attracted the research attention, because the third age today is an important slice of population, in Italy as foreign, and there are many researches on to look for bank this pathology that is becoming increasingly foot in over-seventy population.

Alzheimer's disease is a form of dementia that had an insidious start and a gradual progression. In the course of the pathology we attend the appearance of various types of cognitive deficits, who at first interesting recent memory, and than, during years, we shows language disturbs, difficulty to carry out motor activities and inability to identify objects. Unluckily until today there aren't safe therapies for this pathology, but just symptomatic cures that try to bank the damages causes by disease.

There are different researches on to find new drugs useful for this disease and there have been important discoveries, both in phytotheraphic range (sage and ginkgo) both in pharmaceutic range (new achE inhibithors, briostatine e AF267B).

The most big hope be left the vaccine, in fact there are some founded presuppositions that can open a chink to the discover of a safe and efficacious vaccine for this almost frequent dementia. Furthermore, the genic therapy, that is nerve growth factor, NGF, seem give excellent results in clinical studies too, quickly we can had an eyewash that cure the Alzheimer.

¹ Madeleine Nash, Time, July 2000

1. Neurodegenerative diseases

1.1 Introduction

The neurodegenerative diseases are pathologies that, except in rare cases, developed in senile age in neurologically healthies persons and are characterized by progressive degeneration of specific central nervous system areas. The progressive degeneration seems to be due by interaction of genetic and environmental factors and intrinsic neuronal factors.

The genetic factors be present mostly in hereditaly diseases, for example the Huntington's Chorea, at dominant autosomic character e in so-called "familiar" diseases too, as Parkinson, Alzheimer or Amiotrophic Lateral Sclerosis (SLA).

The environment factors can represent a risk's factor, in fact some ambient toxins, for example MPTP (1-methyl 4-phenyl 1,2,3,6 tetraidropyridine), issues from sintetic heroine, produce damages like Parkinson's disease, but there are reversible. The viral infection, besides, for example the lethargic encephalitic produces secondary parkinsonism. At last, cerebral injury influence the Alzheimer's disease manifestation.

Not be disregarded, besides, the intrinsic neuronal factors, that is susceptibility excitotoxic damage, that I analyze in specific after.

1.2 Neuronal damage

The presence of energetic/metabolic lacks in much neurodegenerative diseases is proved by manifold evidences. In vivo studies with tomography at positron's emission have been displayed the glucose and/or oxygen metabolism alteration into affect areas, at times previous celebrated manifestation of pathology, in Alzheimer's disease (AD), in Huntington's Chorea (HD), in motoneuron bothers and cerebral degenerations.

Furthermore there are watched some zymotic alterations, at mitochondrial level, important for energetic metabolism: for example in AD they observe a redoubt functionality of dehidrogenasi piruvate, dehidrogenasi alpha-chetoglutarate and C cytochrome oxidase. These energetic and metabolic deficits provokes a redoubt production of ATP, who is basic for two pumps working or rather the ATPasi Na/K pump, that rule ionic gradients, shoring up constants, and the rest's potential of neuronal film, and the ATPasi enzymes that limits the active extrusion of citosolic calcium out cell or its storage against gradient (for example in endoplasmic grid). These unbalances can be the reason of neuronal damage, in addiction to the above reasons, because they can create toxic agents, as the reactive oxygen species, or create condictiones that increase the toxicity of mixtures as exciter amino acid.

1.3 The neurodegeneration

The reactive oxygen species (ROS) are involved in very many neurodegenerative disease.² The brain wear out in a large quantity oxygen and this can cause the formation of highly reactive products. These species are normally neutralized by an efficient endogenous antioxidant system, however in some situations there is a displacement between reactive species production and neutralization and it induced the manifestations of pathological events. Among the most important mechanisms involved in free radicals production there are: the superoxide making (O_2^-) and oxygenate water (H_2O_2) by the loss of electrons with high energetic contents from mitochondrial transport's chain; the enzymes activity as monoamino oxidase (MAO), tyrosine idroxilaze and L-amino oxidaze, that have as by-product H_2O_2 ; H_2O_2 production from endogenous catecholamine degradation and ascorbic acid; phospholipase A activation, enzyme that issues arachidic acid, that

² Paoletti-Nicosia-Clementi-Fumagalli, Neuropsicofarmacologia, Edises

produces superoxide anion; the interaction by nitric oxide, NO, and the superoxide anion with the formation of peroxynitrite anion (ONOO⁻), that can transform into a hydroxyl radical (OH^{*}).

The reactive oxygen species interact with basic elements and with an high chemical reactivity, they react with proteins, DNA or lipids caused damage so destabilize cellular entirety. At proteinic level the ROS operate changing covalently the active residues as cysteine thiols (SH) or aromatic hydroxyl. At nucleotidic level they damage, making covalent links, above all mitochondrial DNA, while lipids are oxidized at phospholipids level (lipidic oxidation).

There are many connections by neurodegeneration and neuronal damage by ROS for example in Parkinson's disease and Amyotrophic Lateral Sclerosis (SLA).

“The excess of excitatory amino acid activity, that have normal function of transmitters, may induce neurodegeneration”.³ There are normal amino acids that preside neurotransmission, exciting central nervous system, or rather L-glutamate and L-aspartate, and there are called excitatory amino acids. These would be involved in phenomena based learning and memory processes, but if there are excessively produced can damage nervous cells, in a characteristic way called excitotoxicity. This mechanism establishes itself in few hours and forecasts a depending calcium gear. The excitatory amino acids act starting up both ionotropic and metabotropic receptors. There are three main ionotropic receptors family: NMDA (N-methyl-D-aspartate), AMPA (alpha-hydroxymethyl-isoxazolepropionate) and kainate and the overactivation of these receptors is the most important reason of excitotoxicity, while metabotropic receptors, coupled with G protein and second messenger, seems modulated excitotoxicity strengthening or inhibiting.

In some pathology conditions loss of sodium's gradient or other mechanisms that inhibits the transport's function, promoting the excitatory amino acid accumulation.

³ Paoletti-Nicosia-Clementi-Fumagalli- Neuropsicofarmacologia, Edises

1.4 The Huntington's Chorea

The Huntington's Chorea is a neurodegenerative pathology transmits with dominant autosomic character at complete penetrateness and variable expressiveness. What means dominant autosomic character? One of two parents is carrier or healthy carrier of mutated gene, in this case the stock have the 50% of opportunities to acquire the mutated gene and express disease.

The word "corea" was introduced for the first piece by Paracelso, derives from greek language and means "dance", and is attributed to involuntary clicks of person sick. Was the american doctor George Huntington the first become fond of study of this disease who is characterize by involuntary movments, personality modification and progressive dementia.

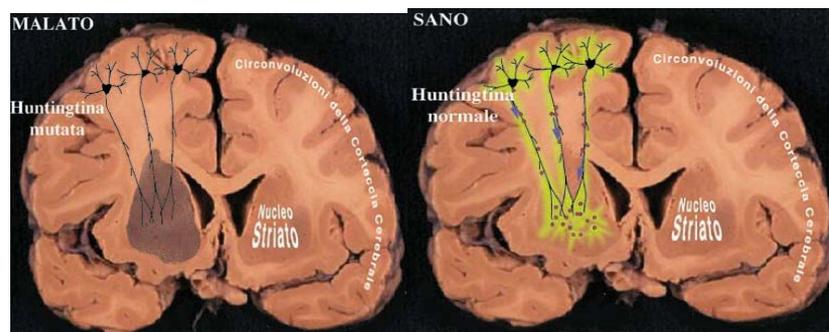


Fig. 1: *Huntington's Chorea damages*

The degeneration is due the alteration of a gene localized on chromosome 4's little arm or rather the Interesting Factor 1 (IT15) gene. The IT15 gene produce a modifield protein called "huntingtina". The healthy subjects had in their DNA two copies of Huntington's Chorea's gene, but in sick person the gene is mutated, in fact huntingtina in subjects with mutated gene have a most long chain (further the forty repetitions cytosine-adenyne-guanyne). To the protein produced by healthy persons isn't successful to give a function, but huningtina "mutated" cause degeneration of brain area that coordinate moviments and base's ganglions, that is caudate nucleus, of putamen and

pale globe, causing apoptosis. The neurodegeneration carry on hitting cerebral cortex, than notching area that presides memory and mind, saving only cerebellum. The mechanisms that bring to neuronal dead are even few known. The hypothesis more elevated may be a glutamatergic excitotoxicity, id est a iperproduction of excitotoxicity amino acid L-glutamate.

The disease, usually, manifests itself in senile age, after seventy years old, but there are early onest too, between ten and fifteen years old. The pathology's progression is so much more rapid as early disease's beginnig and cause dead within 15-20 years.

The Huntington's Chorea manifests itself with various symptoms, both psichics and motors. Symptoms can be divided in two typology: emotional-behavioral, that is an excessive aggressiveness alternating to apathy or depression, and cognitive-intellectual, that is patients begin to loss concentration in futile situations too, to have uncertainty and feeling not be able to carry out the duties more simple and with disease progress they start to lose very short term memory and they aren't able to carry out complicated tasks, even if already made in the past.

The physical-motors symptoms, instead, start to manifest with bream or exaggerate moviments, involuntary ticks or grimages. After begins to underline motor difficulties, involuntary moviments and coordination's loss that interesting all body's zones. With disease progression persons lose tongue's muscle motility, in fact, they toil to speak until to miss word, besides show problems at pharyngeal level, that make too much difficult the swallow.

In the last disease's stage patient enters in a situation called "perpetual motion", or else a bradykinesia's form that patients become at first more slow, then dystonic and finally rigid.

Need to specify that Huntington's Chorea isn't a mortal disease but patients dead for infectious pathology rise up, as pneumonia, cardiovascular complications or wasting due to immobility or difficulty feed themselves.

Therapy for this pathology is only symptomatic, because there isn't way to influence on cognitive deficit or on disease progression and just for this reason that more persons are pushed to precede disease with genetic test (as an alternative TAC or magnetic resonance).

The therapy has the aim to correct both motor signs and psychopathological. Are used as most active drugs in choreas the neuroleptics, that blocks dopaminergic receptors.

The benzodiazepines are used in first manifestations of disease, in fact, they act both on dyskinesias and behavioral disturbs.

Then are utilized neuroleptics, nay aloperrydol, useful in psychotic disturbs too. Is dosed, however, always the minimal dose of efficacious drug, when disturbs are important too.

In the case in which the chorea gives depressionnal conditions, are useful three cyclic antidepressive or fluoxetine. It should be noted that the pharmacologic therapy is always more ineffective with the disease progression, in fact, both in full-blown stage and in terminal stage drugs isn't active, even the most effective.

1.5 The Amiotrophic Lateral Sclerosis or Charcot's disease

The Amiotrophic Lateral Sclerosis (SLA), or Charcot's disease, is a degenerative pathology of central nervous system that hits motoneurons both central, at cerebral cortex level, and peripheral, at encephalic trunk and spinal marrow level.

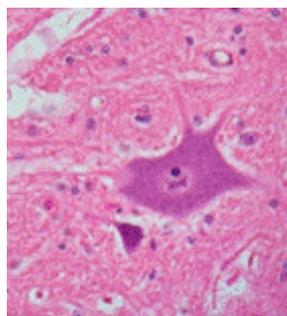


Fig. 2: *A motoneuron*

The neurologist Charcot was the first that described this pathology, but in this moment the pathogenesis is even disown. About the reasons aft hi disease there are important hypothesis, one of these is the discovery of a superoxide dysmutase copper-zinc dependent (SOD-1) enzyme's mutation, important endogenous enzyme that protect from superoxide anion's damages, in 10-15% of patients suffering by familiar SLA have push researchers to study possible oxidative damages in sporadic SLA cases.

Another interesting hypothesis is excitotoxicity damage caused by backlog of L-glutamate, that is the pyramidal way's neurotransmitter, in cerebral liquor .

That is due to a glutamate ricaptation's reduction in motor cortex and spinal marrow of SLA patients, owed by a lower functionally of glutamate's glial transport, for suspect damage to GLT-1 receptor. There are autoimmune hypothesis too on amyotrophic lateral sclerosis pathogenesis.

This pathology is characteristic of senile age and in bigger cases is sporadic, only in 10% of cases is transmit with autosomic-dominat hereditariness.

Symptoms of this disease can manifest time after the disease is present, that is possible because the nervous cells damaged are replaced by that even working, therefore when damages are notables then symptoms start to appear. First symptoms are fatigue and weakness, due to first damages on motoneurons, after appear little muscle contraction or cramps. The first muscles hit are usually hand's muscles, then with time more muscles are feeble. Except ocular's muscles, that there aren't hit by disease

In celebrated disease there is muscle rigidity with consequent dyphagia, difficulty to swallow, and dysarthria, impairment of pronunciation.

Respirator muscle's paralysis is the most frequent cause of dead in SLA patients. Disease flowing is about three-four years.

Diagnosis of this disease is done by electromyography (EMG), to evidence signs of possible neurogenic muscle suffering. Therapies for this disease are studied on pathogenic hypothesis, in fact, were discovered riluzole and the insulin-like growth factor (IGF, myotrophin) can interfere with motor neuron degeneration's process in SLA. For both drugs are pointed out an indicative difference with placebo and, only for IGF, a decrease of functional parameters compromised.

There are, however, symptomatic therapies for SLA and intervene for example on spasticity and cramps with antispastic drugs (for instance baclofen or benzodiazepines).

1.6 The Parkinson's disease

Described for first time by James Parkinson, in a "treatise on paralysis agitans" in 1817, this disease damages dopaminergic neurons in a brain area called "substantia nigra", or black substance, core placed in extrapyramidal system at mid-brain level, in which is produced dopamine, neurotransmitter important for bodily movement too. Is called substantia nigra because, in this place, appear melanin granules responsible of dark pigmentation; melanin derived from phenylalanine and tyrosine, as dopamine. The unbalance between inhibitory and excitatory mechanisms, in which prevail the excitatory, provokes progressive degeneration's symptoms, that is tremor at rest, hypotonia with rigidity, akinesia (loss to movements without muscle force reduction), postural instability, word and writing's disturbs, often anxious-depressive symptoms too. Dementia doesn't represent a classic disease symptom, but it appear in late phases in about third of cases.

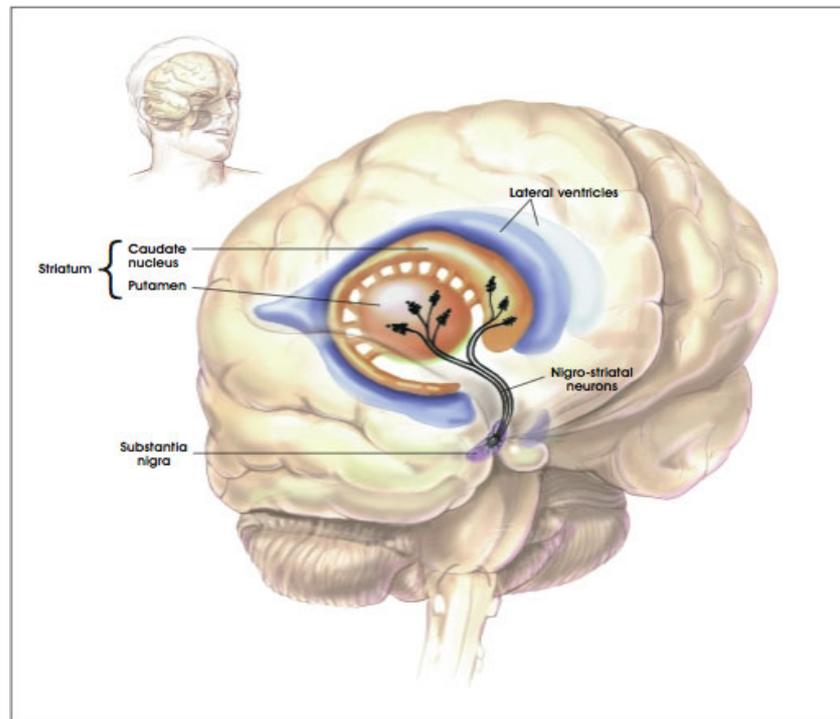


Fig. 3: *Parkinson's disease site*

This pathology attacks more frequently after fifty years old and with a soft priority for masculine sex . Parkinson's disease pathogenesis is considered an whole of factors that may be the cause of first disease's symptoms, as endogenous toxicity and genetic factors.

Endogenous toxicity can manifest with mitochondrial lacks, oxidative stress (as increase of free radicals and decrease of antioxidant defences), excitotoxicity and neurotrophic factors deficiency. As much genetic factors, there are identified some genes that predispose to Parkinson's disease, these genes are classified as "parkina" genes, or PARK, of which exist eleven types. Parkina's genes, PINK-1 (PARK-6) and DJ1 (PARK7) are that with recessive mechanism and their mutation usually define juvenile type of Parkinson, while the alpha-sinucleine (PARK-1) and the LRRK2 (PARK8) are wit dominant mechanism and their mutation is characteristic of late beginning Parkinson.

Genetic factors seem to be influenced by life style, cerebral traumas, ambient toxins (as MPTP, parasiticicide and fungicide), virus (encephalitis or “sleep’s illness”) or drug’s assumption as antipsychotics.

The disease’s classic symptom is tremor at repose, in more of the 70% of cases, above all to hands, but there are other three symptoms that characterize the pathology namely arm and body rigidity, bradykinesia and postural instability. There are secondary symptoms too as dementia, in late phases of disease, depression, in 50% of cases, dysphasia, dysarthria, loss of facial expressiveness and much others .

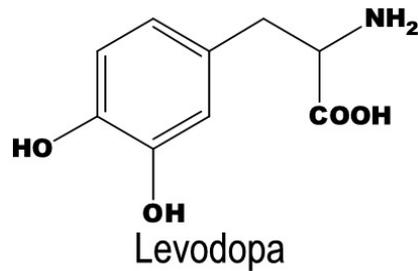
The Parkinson’s diagnosis is founded mainly on clinic exam, or rather neuropathologic exam, with a classification: possible, probably and sure. There are instrumental methods too as functional magnetic resonance, spectroscopy of nuclear magnetic resonance and trans-cranial sonography.

Treatment for Parkinson’s syndrome in last years from a way have been big developments both pharmacologically and surgically speaking, again its conquered an thirty-year experience with levodopa.

Parkinson’s therapy have as intent to readjust derangement between dopaminergic stimulus, come to fail, and cholinergic stimulus, come preponderant. This re-balance can be obtained both reducing cholinergic tone, through muscarinic antagonists, and strengthening dopaminergic transmission, with administration of dopaminergic receptors’ agonists or reestablish of dopamine’s level.

The dopamine can’t be administered as drug because it not manages to overcome the blood brain barrier and then come to brain, and for this reason is administered the levodopa (L-DOPA).

Levodopa is the best drug for treatment of Parkinson’s disease and it is a natural precursor of dopamine, L-3,4-dihydroxyphenylalanine.



To remedy at peripheral level effects provoke by levodopa, it's administers with an peripheral inhibitory of aromatic L-amino acid's carboxylase. This association have great advantages, the first is to increase bioavailability of dopamine at central level, from 1% to nearly totality, furthermore reduces dopamine's collateral effects at peripheral level (nausea, vomit, cardiac anomaly) and reduces daily L-DOPA's doses from grams to milligrams. The DOPA-carboxylase inhibitory more common are carbidopa and benzerazide.

Examples of levodopa and carbidopa associations are: Sirio, that is levodopa and carbidopa methylester, Duodopa, or rather intra-duodenal administration of levodopa and carbidopa, and more others.

Another drug utilized in Parkinson's disease is amantadina, an antiviral molecule who are attributed results to improve neurodegenerative symptoms of disease, above all tremor. It has smaller efficacy regard levodopa, above all in long term therapy, but however it's utilized in association both with levodopa and with anti-cholinergic drugs, so it has action both tremor and bradikinesia

Dopaminomimetics, in other words dopamine's agonists drugs, simulates dopamine effect and compensate of it then the lack at cerebral level in parkinsonian's patients. Their function are to act as "false keys" that brain accept as original. This drugs, for example bromocriptina, pergolide or apomorphine, must be administered with caution because can involved problems at gastro-intestinal level, as nausea or vomit.

Drugs COMT's inhibitory, or rather cateto-O-methyl-transferasi enzymes responsible of dopamine and levodopa degradation, as the moclobemide, are utilized in Parkinson's disease to extend action's duration both of dopamine, in case of administration, and levodopa blocking enzymes.

Finally last drugs utilized in Parkinson's therapy are the anticholinergic drugs (hydrochloride biperidene, hydrochloride bornaprina, methixene, orfenadrina, prociclidina). This drugs are administrated to reestablish unbalance created, in fact, is banked the acetylcholine's excess and it try to regulate the neuronaltransmitter's functioning, disturbed by dopamine want.

Parkinson's surgical therapy start to be ponder after 1942, happened, in fact, that during a neurosurgical on a parkinsonian patient, verified an intrasurgical complication, the accidental closing of an artery, with immediate damage of thalamus and consequent tremor vanishing.

Lately this therapy is returned because parkinsonian patients often can present syndrome due to a long period treatment with levodopa and this provoke an accentuation of some disease symptoms, as rapid passage from OFF period, or rather of muscular intense block, to involuntary movements often impairing. Into 50' years was introduced a new intervention's method, in other words the "stereotoxic" technique, this technique allow to individualize and operate on a specific brain point, with radiologic techniques and a millimetric precision.

This surgery therapy is advised for those patients that answer good to drugs but that suffer of OFF period impairing or stultify, or involuntary movements intense and disenable, with preferably age upper the seventy years old, that had a good clinical square and hadn't in their history psychiatric problems.

A novelty in Parkinson's disease range, in initial phases, is the discovering of Q10 coenzyme⁴ utility, called ubiquinone, in therapy. Studies compared to placebo showed that Q10 coenzyme

⁴ <http://www.neurologia.it/2002/10/15.html>

after sixteen months of treatment slow down the neurodegeneration of Parkinson's disease, now there are even studies ongoing to testify its efficacy.

2. The Alzheimer's disease

The Alzheimer's disease is a progressive and degenerative pathology of central nervous system and it's the most frequent human dementia's form. It takes name from Alois Alzheimer who was the first in 1907 that described disease's symptoms and neuropathological aspects, that damages progressively cerebral cells.

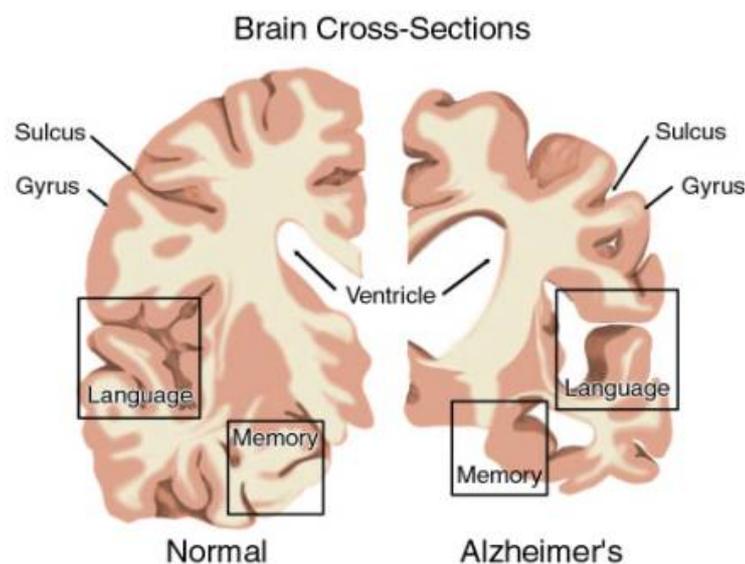


Fig. 4: Brain's areas hits by Alzheimer's disease

In past, was utilized expression "Alzheimer's disease" concerned to a pre-senile dementia, as opposite to senile dementia. Today count itself, instead, that disease hit persons under sixty five years old and persons over sixty five years old. Therefore, today, they refer often to disease as an Alzheimer's dementia, specifying, eventually "at early beginning".

2.1 Symptoms

The symptoms can do suspect the onset of neurodegenerative pathology, classified by Alzheimer's Association, are ten: lapses, difficulty to do known conventional, linguistic problems, spatial and temporal disorientation, loss of judgement ability, difficulty of abstract reasoning, objects' loss, sudden changes of humor tone, personality changes, initiative's loss.

Now we analyze these symptoms more into specific:

- The lapses; normal is to forget something but when these became a problem for elderly people, for example they interfere on work, then necessity making suspicious, if, besides, there re difficulties to do simple actions, for example if subject shows difficulty to button shirt or to tie shoes, should be apraxia's symptom, one of Alzheimer's symptom.
- Linguistic problems can be normal, happen at all to forgive a word, but it became a recurrent problem should be anomia, inability to recognize the names of objects or people.
- The spatial and temporal confusion is normal if we mistake day of week or month, became strange wrong the year or month, while the spatial confusion is a symptom, if we point out confusion or poor memory respect to familiar places.
- The loss of judgement ability can manifest with inappropriate dress' manner, loss thing's value, make wrong judgement or express in wrong way; besides can verify abstract reasoning's difficulty too, then difficulty to do mathematic operations or simple arguments.
- Confusion, then loss things, can be a symptom of disease, for example leave keys in the fridge.

- Characteristic's change, as sudden humor changes, or personality, as aggressiveness, eccentric characteristic or paranoiac symptom.
- Interest's loss, is normal that an old person is few stimulate to word that surround him, but isn't normal if he miss fully motivations and wish to do, could be a disease symptom.

The celebrated disease's symptoms are various and are the manifestation true and real of first symptoms just described, in fact, isn't simple ascribe this signs to Alzheimer's disease because there are any pathologies too, that have similar symptoms as depression or multi-infarcted dementia.

Anterograde amnesia is one of most important symptom of Alzheimer's disease, and is the subject inability to remember recent events, or better recent events happen after disease onset. Patients hit by Alzheimer draw to have good long term memory, then remember for example childhood, but very bad short term memory, then the incapacity to remember events successes recently .

Other symptoms are apraxia or rather the incapacity to do common actions, as for example whistle, mouth-facial apraxia, doing coffee, cocking, doing sketches; the agnosia or rather inability to recognize common objects. Could be a dissociation among animate and inanimate objects: Alzheimer's patients extend to have problems with inanimate objects, as fruit or vegetable, and/or animate objects, as animals. However during disease diagnosis is important distinguish if patient can be hit by agnosia, in which him doesn't recognize object, and anomia, in which he recognize object, but doesn't remember the name, in fact, usually, subject uses synonymous, assonant terms or neologisms to define object of which doesn't remember name.

Besides subject, during diagnosis, is submitted at some questions to define his spatial-temporal confusion; questions are “what day is it?”, “in which month are we?” ,”what year is it?”, while as it regards spatial confusion set question “where do we find now?”.

Other symptoms are acalculia, in other words subject doesn't succeed to perform elementary arithmetic operations, agraphia, in which patient have problems with writing, in serious cases he doesn't succeed even to write his signature, besides manifests intellectual deficits, that is patient doesn't succeed in sustaining reasoning.

Subject manifest sudden changes of humor tone, that is depression, euphoria, weeping; is common the manifestation of anxiety, nervousness and insomnia too.

Besides patient could be assume some behaviors more different in comparison to pre-morbid, for example increase of aggressiveness. Psychotic's symptoms most common could be hallucinations, paranoia and not real thoughts, also this symptoms are few frequents of behavioral symptoms and they manifest in disease's late phases.

2.2 The causes

The Alzheimer's disease (AD) is the principal dementia cause and of cognitive decadence in senile population. Disease manifest itself with neuronal and synapses loss and with extracellular deposition of amyloid substance and intracellular neuronal fibrillary skeins. This alterations are retentions essential for disease diagnosis and had toxic effects on neuronal cells that progressively died also in consequence to cerebral deposition of these substances. Progressive synapses and neuronal loss have with time as consequence the appearance memory's alterations of cognitive ability and of behavior.

There are other mechanisms that induced neuronal dead, what for example a microglial cerebral cell iper-activation that produce substances with pro-inflammation activity.

The Alzheimer's causes are still unknown but there are some hypothesis on dementia pathogenesis. Isn't excluded that two or more hypothesis could combined to constitute Alzheimer's disease pathogenesis.

2.2.1 Genetic hypothesis

Genetic mutation seem be a cause of Alzheimer's disease insurgence, in fact, thee are scientific studies very accurate to evidence as some mutations seem be degeneration cause .

The gene denominate apolipoprotein E epsilon-4 (apoE-e4), 19 gene variant, is present in 15% of sane population and in 50% of cuts population and seem that its polimorfism united to cardiovascular problems, as hypertension, and cholesterol increase, can be cause of disease insurgence. This varying is being considerate as a genetic risk's factor.

“The possibility that the risk for Alzheimer's disease can be reduced by diet or lifestyle is of great importance and suggests a preventative treatment in Alzheimer's disease”⁵, in fact has been approved that a lipid poor diet and cholesterol reduce risk to manifest Alzheimer's disease and cardiovascular pathologies too.

We can affirm that a diet rich in lipids, more-unsaturated acids fat with long chain deriving from fish's oil, genotype apoE and cholesterol are correlated with Alzheimer's disease.

5

http://www.ncbi.nlm.nih.gov/pubmed/18378224?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Other mutations that it was found are on called amyloid protein's gene (APP) on chromosome 21, and it's responsible of the amyloid protein's gene formation, the presenilina I (PS1) foresees on 14 chromosome and gene of presenilina II foresees on chromosome 1.

The APP mutations are rare, only twenty families identified all over the world, and they usually cause disease precocious debut, 35-40 years old. Around one hundred thirty PS1 mutations is been individualized in patient with precocious Alzheimer, in fact, these two mutations are characteristic of disease precocious debut (28-70 years). Thin to today only nine PS2 mutations is been individualized, always verifiable in precocious Alzheimer patient, but also late after 80 years.

APP, PS1 and PS2 mutations cause an increase in the production of beta-amyloid, amyloid pltes constituent, while the apoE don't cause an increase of production but an increase of amyloid's accumulation in extracellular space.

Possess apoE gene doesn't implicate the disease demonstration, but it constitutes a remarkable risk's factor, in fact if they are inherited a single allelis e-4 of the gene, increase the risk, while if two allelis e-4 are inherited, the risk increase of eight times.

Other possible genetic risk's factor are: ACE enzyme, Angiotensina inverting enzyme, that converts the angiotensina I in angiotensina II on chromosome 17, the methylenetetrahydrofolate reductase (MTHFR) gene on chromosome 1, the endothelial nitric oxide sintasi on chromosome 7, and the tied up metabolitis derived from beta-amyloid metabolism: alpha-chimotripsine, alpha-ACT n chromosome 14 and alpha2-bigglobuline (A2M) on chromosome 12, the low-density lipoprotein receptor-related protein (LRP1) gene on chromosome 12, the transcription factor LBP-1c/CP2/LSF gene on chromosome 12, the gene for butyrycholinesterase (BchE) on chromosome 3, the bleomycin hydrolase (BH) gene on chromosome 17, the polimorfismis at promoter's region level of gene apoE-49 A/Ts and -219 T/Gs on chromosome 19, genes tied up at inflammatory theory: the

interleukine-1-alpha gene on chromosome 2 and for interleukine-6 on chromosome 7, the tumor necrosis factor alpha (TNF-alpha) gene on chromosome 6⁶.

These genes just listed are denominated susceptibility's genes, in other words the presence of these genes involves an increase of susceptibility at Alzheimer's disease.

2.2.2 Viral hypothesis and bacterial hypothesis

In absence of a certain cause you cannot be excluded that disease has viral origins, even if there are no clear signs around hypothesis.

There is a bond among Chlamydia Pneumoniae, a common respiratory bacterium and Alzheimer's disease. The bacterium, that can spread in different organism's place among which the central nervous system, has, particularly, a bond with amyloid plates verifiable in people's stuck by the not-hereditary Alzheimer's disease.

This has been established with a study conducted by researchers of Philadelphia College of Osteopathic Medicine's Center for the Study of Chronic Disease of Aging and published on the magazine "Neurobiology of Aging". The bacterium, as already in relief in a preceding search, it is present into brain of 90% of Alzheimer's disease patients. In this study have observed tha injecting bacterias in the nose of mice without predisposition toward amyloid plates accumulation, the progressive plates' deposit themselves has been caused instead, producing so a partial model of the Alzheimer's disease. According to these researchers the Chlamydia could be the pathology's primer. This theory goes to support the infectious hypothesis that had been proposd for the Alzheimer's dementia.

⁶ S. Sorbi- Genetics of Alzheimer's disease - Neurol Sci (2003)

2.2.3 Aluminum's hypothesis

The aluminum for many years has been considered an harmless metal and therefore broadly used, in the last years, however has been underlined that this metal develop a critical role in Alzheimer's disease pathogenesis. Underlined its probable toxicity, it rises evident the necessity of a narrow control of aluminum pollution to drastically reduce its toxicity.

It is present, for example, in the drinkable water, in the tea and digestive tablets, even if its presence in water remains the most potentially harmful. In fact, control should be had on water sources in great cities, above all on sources destined to children's feeding, insofar the greatest brain aluminum's accumulation is had in first age's years, very harmful accumulation then in senile age.

Aluminum salts' accumulation on cerebral cortex, observed in animal experiments, it produces neurofibrils' skeins.

Today, however, there aren't sure tests that an aluminum poisoning involves in the future the manifestation of Alzheimer's disease, but this hypothesis is supported by presence of aluminum's accumulations in cerebral tissue of Alzheimer's disease patients.

2.2.4 Immune system's hypothesis

According to this hypothesis the immune system would selectively attack the acetylcholine's neurons. In fact, has been hypothesized that the organism begins to produce antibodies in great quantity and auto attacks acetylcholine's neurons, this until when neuron is not able to develop its physiological activity reaching necrosis.

“More marked alteration of immunologic answers, both cells and humoral, have been underlined in AD patients, in comparison to the healthy controls. They seem to point to immune system in AD pathogenesis:

1. The amyloid nature of senile plates's core, that is generally accompanied to immune system's illnesses;
2. A great frequency of immune system illnesses, in familiars of these patients;
3. The presence of autoanticorps against the neurofilamentis and, above all, against the manufacturing prolactine's cells, present in a tall percentage of patient (around 90%) and in the trisomia 21's subjects".⁷

2.2.5 Oxidative hypothesis

The oxidative hypothesis is found on damage caused by free radicals. The free radicals can determine very harmful chemical reactions for cells, with uncontrolled oxidations, that can damage the metabolism, the structures and neuronal functions, up to cause its death. This hypothesis could be reasonable for Alzheimer's disease.

2.2.6 Others hypothesis

Epidemiological studies case-control have shown a taller risk to develop AD in subjets that have suffered serious cranial traumas. And' is also shown that repeated cranial trauma can provoke tissue alterations similar to neurofibrils degeneration, the so-called "punch-drunk syndrome".

There is a emato-encephalic barrier hypothesis in which an altered brain permeability would allow toxic substances to penetrate inside brain and have their toxic action and attack, therefore, neurons.

⁷ <http://www.salus.it/neurologia/alzheimer.html>

2.3 Physiopathology

The Alzheimer's disease is characterized by formation, at cortical level, of amyloid's plates and neurofibrils' skeins. The presence of these microstructures and their recognition represent the only tool to diagnose with certainty the disease.

2.3.1 Amyloid plates

The amyloid's plates or senile plates, are the classical disease in progress symptom and they are mainly constituted by amyloid.

These plates, present in blood vases and in meninxes, are constituted from axon's units, dendrites and altered glial cells that they wind a core formed by beta-amyloid all we produce amyloid, but sometime it forms aggregates called fibrils, that than they unites together to form amyloid plates.



Fig. 5: *Amyloid Plates*

The amyloid is a fibrillary protein with dimensions of 10 nm that accumulates, locally or in diffused way, forming some deposits that are at the start of amyloidosis and of Alzheimer's disease. This protein distinguishes itself from a lot of other substances because it's insoluble in common salty solutions and it's resistant to proteolytic enzyme's action and to the phagocytosis.

To underline it in champions of tissue Red Congo is used and it's observed to microscope with polarized light. Around the 10% of amyloid's deposits is constituted by C reactive protein, normally present into blood, that increases the inflammatory stadiums, in fact, an excess of this protein in blood can be amyloidosis symptom.

The amyloid's protein precursor is the amyloid precursor protein (APP) codified by chromosome 21 and is a normal constituent glycoprotein of human brain. The enzymes alpha, beta and range segretasi of beta-amyloid takes, through division, to the formation of amyloid present in senile plates of Alzheimer's disease with B-sheet configuration. The beta-segretasi enzyme particularly it's the responsible of production of beta42-amyloid, the protein most present in senile plates.

The protein accumulates because to the place of ordinary refolding there is also a trial of misfolding that it favors the accumulation of the protein.

The amyloid plates are extracellular heaps of assonal, dendritic and glial united to amyloid proteins. These accumulations that are formed in the extracellular cerebral tissue are, in healthy people, quickly polished up. The fibrilles formation is a nucleation-dependent process, in fact, too much saturated solutions of amyloid peptids extend to join, but the process can be accelerated if are added to the solution some small fibrilles of preformed amyloid.

Has been underlined that people that have suffered a serious cranial trauma have high-levels, if also transitory, of beta-42 after a week from the event. This transitory presence could be remarkable in the patient's future and to favor the disease demonstration.

The typical signs of Alzheimer into cerebral tissue, that is presence of amyloid's plates and neurofibrils' skeins, have more evident effects in women, that develop more than men insanity's symptoms and others clinical disease aspects.

“From laboratories of the Scripps Research Institute of La Jolla, in California, comes the confirmation that the cannabinoidis, the active principles of marijuana, can act both on symptoms and on th progression of the Alzheimer’s disease. The researchers of the Scripps Research Institute- a biomedical organization no profit among the most important of the word- have shown that the delta-9-tetrahydrocannabinolo (THC) inhibits the formation of amyloid’s plates, considerate the primary pathological marker of Alzheimer’s disease: the THC would have an inhibiting effect on the union of beta-amyloid superior peptide to that of the drugs actually in use. Particularly the THC inhibits the acetilcolineesterase enzyme (acetilcoline’s degradation responsible) that acts as one molecular “chaperone” (assistant) to accelerate the amyloid’s plates formation in patient’s brain ”.⁸.

The correlation between the plates density and disease presence is not possible since in all the elderlys there are amyloid’s plates accumulation, the only difference it’s that Alzheimer’s patient have thick accumulations in cerebral cortex and hyppocamp.

2.3.2 Neurofibrils’ skeins

The neurofibrils’ skein are bundles of filaments into neurons cytoplasm that displace or wind the core and they accumulate as skeins in cellular body. Usually its accumulates in great dimension neurons as in hyppocamp, in the smelling cortex, in amygdale, in pro-brain’s basal nucleus and in more trunk’s nucleus, inclusive locus coruleus and rafe. From the ultrastutturales point of view its appears as bounded of coupled helical filaments (CHF) and every filament is constituted by two fibrilles prepared to helix. A base CHF component is givn by anomalous iper-phosphorilate forms of tau protein, a assonic protein partnership to microtubulis that increase their assemblage. These heaps are rich of tau protein and they also contain ubiquitina, especially in great neuronal loss areas.

8

http://www.lastampa.it/_web/cmstp/tmplrubriche/scienza/grubrica.asp?ID_blog=48&ID_articolo=46&ID_sezione=71&sezione=

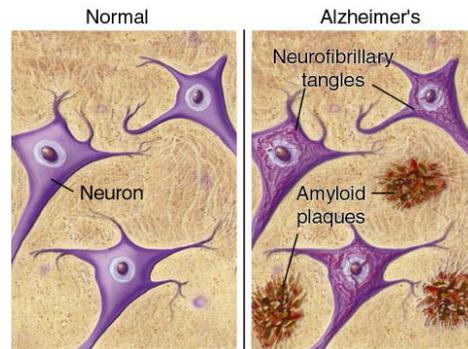


Fig. 6: *Neurofibrils' skeins*

The tau protein gene mutation, that coding for the constituent protein the heaps, are fundamental for the skein's formation. The spherical bodies of the healthy neurons are covered by neuritis that form connections with other cells. These neuritis wind a structure inside called microtubules, that gives its form to neuron and it allows the transport of nourishing and chemical substances: the adhesive that holds united this system is tau protein.

Under physiological conditions the tau protein is on microtubulis and firmly holds them united, instead when Alzheimer's disease rises up the proteins detach itself and begin to join among them, forming tangles. Contemporarily the microtubulis are broken up and neurons dies.

Experimental observations have shown that neurofibrils' skein have a remarkable importance into progress of the insanity, while the amyloid plates is also been found in elderly healthy.

2.3.3 Cerebral Atrophy

“The meeting place volume or atrophy of some cerebral zones what amygdala and hyppocamp could be the signal that elderly people in good health will develop, in the turn of few years (at most 5 or 6) Alzheimer insanity or disease. And' how muchi t emerges from the results of a new study published on Archives of General Psychiatry megazine.

Precedent studies had already underline that Alzheimer's patient or in cognitive decline, light too, manifest reduced volume of amygdala and hyppocamp. These researches didn't have

nevertheless shown that the measurement of cerebral atrophy effected with manetic resonance could foretell the rise up of such pathologies before if they manifested the symptoms of it".⁹

The Alzheimer's patients manifest one pronounced cortical atrophy. The more stricken cerebral zones are the frontal lobe, the anterior part of the temporal lobe and he wall lobe. The hyppocamp is very stricken from the atrophy.

Are interested locus coruleus and limbic areas too, probably cause humor's disturbs, and the Meynert basal core.

The Meynert's nucleus degeneration can explain the serious diminution of acetylcoline concentration in the cortex (60-70% of cortical activity).

2.3.4 Sinaptic degeneration

In individuals' brain struck byAlzheimer, finds sinaptic structures' de generation: there is a diminution of colinergic sinapsis and lack of protein substances present in sane cell's sinapsis.

The of the availability of acetylcoline and the colinergic sinapsis efficiancy precedes the degenerative picture evident hystologically, for the deposit in pre-sinaptic and post-sinaptic areas of amyloid precursors.

The degenerationhas a good correlation with the disease elapsed and entity. The demential symptoms could be interpreed as a result of sinaptic's deficit, because neurons have difficulty to communicate.

⁹ Den Heijer T, Geerlings M, Hoebeek F, et al. Use of Hippocampal and Amygdalar Volumes on Magnetic Resonance Imaging to Predict Dementia in Cognitively Intact Elderly People. Arch Gen Psychiatry 2006;63:57-62.

2.3.5 Congoile Angiopathy

It is the deposition in the wall of small cerebral vessels of betaamyloid protein and it causes an increase of the leptomeningeal and intracortical arterioles walls and formation of double helix filaments, constituent of neurofibrils' skeins. .

2.3.6 Neurotransmitter's degeneration

The cholinergic system, the more struck by Alzheimer's disease, goes toward to subcortical cholinergic neurons atrophy, basal nucleus, due to:

1. Diminution of cortical level of ChAT, correlated with cognitive deficit
2. Diminution levels of AchE
3. Diminution expression of nicotinic and muscarinic type M2 receptors

Besides there are a diminution of serotonergic system expression at cortical and hippocampal level and a diminution of neuronal loss, of noradrenergic system, into coeruleus locus.

More there is excitotoxicity caused by glutamic acid production, a malfunction of GABA receptors and of some neuropeptides as the substance P, oxytocin, the AUP and the CRF .

2.4 Epidemiology

Estimates that in the world around eighteen million people is stricken from Alzheimer's disease, of which around a million in Italy. The Alzheimer's dementia, and other insanities, represent one of the most important disability's causes in elderly and it's one of the principal sanitary and social problem correlated to the aging, both for quality and quantity of assistance required by the patient, that for the involvement of medical, social and economic order.

Tab 1. Prevalence (rates %) of Alzheimer's disease in Italy in base to the sex and age's band :

	65-69	70-74	75-79	80-84
Men	0,5	0,8	2,9	5,8
Women	0,7	2,4	4,3	9,5

Source: ILSA's (Italian Longitudinal Study on Aging) study – 2000/2001

The prevalence approximately doubles every five years of age, at least between the 65 and 85 years old. The specific prevalence for age's classes between the 1% in subjects of age of 65-69 years, and increase to 40% in age's group both 85 and 89 years, according to some studies.

The almost exponential prevalence growth in the band that inclusive age between 65 and 85 years has made to hold in past that such pathology could be almost inevitable in advanced ages. In reality the studies until now ducts are relatively characterized for a scarce champion's numerousness to the classes of more elderly age, with consequent great results variability.

This prevalence's doubling over 85 years remains therefore to confirm. Preliminary analyses seem to point out the possibility of a deceleration of such growth after 85 years and a point of bending to 95 around a 40% rate.

To forehead of numerous prevalence's studies, often exist few studies on the dementia's incidence and with conflicting data. The incidence's studies are generally very expensive, they ask for a prolonged observation in the time, repeated measurement, numerous population champions an relatively stable, an accurate diagnostic evaluation, limited losses to follow-up. Some reasons that can explain partly the differences relief in different studies concern the study's champion composition, the precocious cases' diagnosis, the inclusion of light and moderate forms of dementia, the use of tools' screening with different sensibility and of different diagnostic criterios.

The increase of insanity's incidence with the age is brought in all the studies: the annual incidence's rate is estimated in around 1% in subjects over 65 years, varying from 0,2/0,8% in subjects of age inclusive between 65 and 69 years, up to more than 3% in subjects over 80 years.

In Italy therefore the risk both Alzheimer's disease that vascular insanity exponentially grows with age's increase, but with precise differences among the two sexes. This suggests that hormonal factors and life style can have an important role in etiopathogenesis of dementia principal forms.

The data until here brought show that the epidemiological search on insanity is well distant from the exhausted possession its potentialities. The actual epidemiological and biological knowledges suggest that insanities in general, and Alzheimer's disease in particular, are the pathologies with a long pre-clinical phase, in which various interventions directed to prevent the disease development.

According to this theory, the plates and neurofibrils alterations of Alzheimer's disease are the result of a complex interaction among genetic and environmental factors. All of a sudden celebrate alterations of disease progress independently.

The clinical symptoms appear when sinapsis number goes down under a certain threshold, or when acute events or stress overcome cerebral ability to answer in effective way. The lower education's level and reduction of intellectual activity in advanced age can contribute to synaptic reserves diminution

2.5 Prevention

Prevention to Alzheimer's disease manifestation is very important for a pathology that is becoming always most common in over-eight age's range. There aren't cures, in fact, the drugs are

only symptomatic and the research on a possible vaccine is still in progress, then, if possible, it needs prevent manifestation of this weakening pathology.

2.5.1 “Missing smells” test

A test that could be effected for preventing Alzheimer originates from American College of Neuropsychopharmacology (ACNP) and is denominated the “missing smells” test. It would seem in fact that administrating subject at dementia’s risk to this test it could be prevented the disease manifestation. The test consist in “smell” ten fragrances (lemon, carnation’s flowers, kin, menthol, smoke, gas, soap, pineapple, wood’s fruits) for about eight minutes. The patient that doesn’t repeatedly succeed to recognize well the odors it has a taller risk to develop disease after five years. This research has been effected on around one hundred fifty patient with cognitive problems for about 6-11 months, and it seems to have given good results ¹⁰.

2.5.2 Obesity and lifestyle

The research of the last years has underlined that the same factors that favor the cardiovascular disease , involve also a great risk for Alzheimer’s disease: obesity, tall cholesterol and hypertension are risk’s factors modifiable today. Recognize and treat them probably reduces the risk to manifest the disease. Currently the principal search interest turns to pathology prevention, that is characterized by a long preclinical phase that last up to 20-30 years. Modest interventions (nourishing, pharmacological or influencing on risks factors) could prevent onset of dementia in a great number of people.

¹⁰ Ansa, 14/12/2004

When the disease manifests itself in clinical way, the trial is already advanced. From aside this circumstance makes more difficulty the therapy for the one who is ready patient, from the other side it offers the great opportunity to intervene before the clinical demonstration and to prevent, in this way, many cases of disease.

A recent discovery affirms that the “monster of Gila” possesses an essence that can positively intervene on the cognitive abilities. That the SALIVA of this reptile is discovered, for giunta poisonous, if drawn in drug, can oppose Alzheimer’s effect. The search’s staff is American, for the exactness in New York, and are able to extract this substance from the saliva produced by Gila’s Monster (*Heloderma Suspectum*) that acts on the brain’s receptors.

For now the drug produced by this substance is experimental, but it’s giving good results with the animals, improving notably the cognitive faculties, especially those tied up to memory and learning use. If the experiments will keep on giving positive results, it’s thought that within the end of the year, the drug can be experimented on human.

“The American Journal of Medicines” affirms that a subject that consumes fruit’s juices or vegetable’s centrifuged at least three times to week has the 76% of inferior risk to manifest Alzheimer’s disease. In a first moment was thought about the antioxidant activity of vitamins C, E and A present both in fruit and vegetable, but subsequently this news as been denied and this preventive power is attributed to the polifenolis, in other words of most present antioxidant in juice, centrifuged, into tea and wine, or better in grape.

A diet rich in fat acid Omega-3 containing in food, known also as DHA, can help us to prevent the Alzheimer’s disease, even if is carriers the gene that make us vulnerabilities to disease. The amazing discovery is work of a research’s group of University of California, to Los Angeles, driven

by Greg Cole, thanks to studies ducts on mice. The researchers have raised some mice carriers of the gene known for the characteristic to cause brain's lesions as the Alzheimer's disease. The native intention of researchers was to appraise as the various environmental factors influences the symptoms of dementia in the time. The mice have shown to have memory problems and other typical Alzheimer's symptoms in very smaller measure in comparison to the expectation. This can be attributed to a diet rich in soy and fish, two foods rich in DHA.

Lower part levels of the vitamin B12s are in partnership to worse results in the tests that measure memory of the elderly ones that have a genotype that predisposes them toward Alzheimer's disease.

It's how much results from a study published on Neuropsychology. The genotype in matter, the allele epsilon-4 in the apolipoproteina E's (APOE) gene, is present in around the 15% of the people and it is a factor of risk for the insanity. The search points out that almost a person on four among those people that have a copy of the allele 4 and almost halves the people that have two copies of the allele 4 it will develop the Alzheimer's disease. It's already known to the search, besides, that low levels of two vitamins B, B12 and folatis are tied up to a diminution of the memory and a great risk to be stricken by the Alzheimer's disease.

The study of C.Y. Lee of the Cornell University affirms that "an apple a day, or also more, better if fresh and redhead, removes Alzheimer return." In fact has been underlined that a present substance especially in the red apples, and also in onions and blueberries, the oaketine has a strong effect antioxidant and prevents the free radicals. The oaketine, therefore, would prevent the illness guaranteeing a good health of the brain.

The elderly ones that good habit has to take long walks will have less probability than to suffer from the insanity caused by Alzheimer in comparison to those that have the tendency to be

sedentary. Already note for the ability to protect our health against cardiac illnesses, crab and diabetes, a moderate and to regulate physical activity seems to be able to reveal a medicine by protective effects for the cognitive functions, the true aching key for the health and the quality of the life in advanced age. Robert Abbott is to draw this conclusion, biostatistic of the University of Virginia Health System, after the study medical duct in the Hawaii on 2.257 men of inclusive age between the 71 and the 93 years. From the study he has emerged that those people whom were more idlers had 1,8 times probability in more than to develop the Alzheimer in comparison to the men that walked more.

A new study has reached the conclusion that the obese women for the greatest part of their life with a great probability will suffer from a loss of cerebral tissue, one of the first signals of the risk of dementia, or of Alzheimer's disease. The study, conducted in Sweden and published on the magazine Neurology, has involved 290 women of inclusive age between the 46 and the 60 years and it refers to a period of 24 years of observation with the effected computerized tomography every six years to examine the cerebral tissue, which the measurement of the body is added mass index (BMI), or rather the index of bodily mass. From the observation of the data has emerged how more elevated it was the women the body mass index, therefore the women were anymore overweight or obese, great the probability of a reduction of the cerebral tissue results. This makes evident that the obesity besides causing problems to the cardiovascular system as diabetes and hypertension, and for such to increase the risk of insanity, can increase by itself the secretion of the chortisol, hormone that can bring to the cerebral atrophy.

A news of July 2007 affirms that consuming "curry" the Alzheimer is prevented. A search affirms that isolated the bisdemethoxycurcumina, active principle of the curcuminoidis, that is a natural substance coming from the rhizomes of the *Curcuma Longa*, it could help the immunitary

system to eliminate the beta-amyloids. It is discovered that it would stimulate the macrophages and therefore to avoid the accumulations of amyloids.

2.6 Clinical course

The clinical elapsed of disease has been divided in phases, this to make simpler to the eyes of the relatives of the patient of the to evolve some diseases. We say that the disease generally has an elapsed of maximum fifteen years. We can individualize three principal phases of the disease: light, moderate and serious insanity.

The light insanity, which has lasted since two to four years is characterized by troubles of memory, as to forget the names and the telephone numbers, but, due to the non serious nature of these signs, can pass unnoticed or as natural consequences of the age to be justified. The progressive loss of the memory, that recent, can interfere above all with the normal carrying out of the daily appointments. The subject has difficulty to orient in the space and in the time, can for example have problems to find again the road of house. Also the language starts to be compromised: difficulties appear to produce sentences suitable to support the thought, frequent breaks they are used for incapability to "to find the correct word". The humor becomes more depressed following the awareness of the proper progressive disability, or the reaction can be characterized by aggressive and anxious demonstrations.

The moderate insanity with duration two-ten years average is generally temporally the more lasting phase, and is characterized by an aggravation of the symptoms introduced in the preceding phase. The forgetfulness are meaningful more and more; it increases the incapability to remember the names of the family ones with the possibility to confuse them, as it increases the spatial disorientation and storm. In this stadium the necessity of supervision and assistance in the daily

activities it does him more urgent, the patient curtains to neglect his own aspect, his own diet and the daily activities; the throngs of the humor and the behavior become more remarkable.

Serious insanity has lasted three years average and it is the terminal phase of the illness during which the sick person is completely dependent and asks for continuous and total assistance to sustain in life. And it's characterized by a total loss of the ability to speak and to understand, is able however to be maintained up to this phase the ability to express emotions through the face. The subject totally becomes incapable to recognize the own familiars, to complete the daily actions of the life as to dress, to eat, to wash himself, to recognize his own personal objects and his own house. The movement is totally by now compromise up to the allurements, there is no anal control.

2.7 Diagnosis

The certain diagnosis of Alzheimer's disease can have also with the comparison of the amyloid plates and of the neurofibrils' skeins, and it implicates therefore the biopsy post-mortem. The medicine has set a series of test of evaluation that allow, together with an accurate anamnesis, to understand if the problems accused by the patient are referable to Alzheimer, or to at another form of insanity.

The patient conditions are valued, of the accused symptoms and of their elapsed storm, his relatives and the familiars are interviewed, to have further details on the changes of its personality, and in its behavior. At the same time they are performed diagnostic (examinations of the blood and diagnostic for images), test that allows to identify possible causes of insanity not Alzheimer, or to notice other pathologies that cause cerebral damages as tumors or heart attacks.

A test that gives certainty of Alzheimer's disease doesn't exist, the diagnosis is made for probability excluding other causes of insanity. You founds on:

1) check of the state of insanity with test psychometric specific;

2) presence of serious memory's deficit;

3) observation that the memory's deficit and the insanity quickly are not insurgent or acutely but during a period of years.

It needs to exclude for the diagnosis of Alzheimer's disease, that the symptoms are insurgent associates to motor or sensitive deficit or to dizziness and signs of the equilibrium modification. Subsequently they are effected instrumental (TAC, RMN) checks that will underline the atrophy of the cerebral cortex.

The clinical signs that allow the diagnosis of the illness are: the accented losses of memory, the feeling of dismay also in the family environments, the problems to manage his own finances or to complete the normal usual daily activities, a great difficulty to take decisions, the loss of spontaneity and sense of initiative and the increase of the anxiety.

An experimental test, based on the analysis of the cerebral-spinal liquid, could help the experts to precociously identify of Alzheimer's disease. The novelty arrives from a study conducted by researchers of the University Hospital in Geneva in Switzerland.

Currently the physicians are able to recognize Alzheimer's disease from the observation of the symptoms, as for instance the loss of memory and the confusion state of the patients. You disturb that however they are common to other forms of insanity. The only certain diagnosis is gotten with the autopsy. In the study, the researchers driven from Odille Carrette, they have examined the cerebral-spinal fluid of 10 patients with symptoms connected to the Alzheimer and of other 10 people that didn't show characteristic signs of the illness.

Thanks to a particular technique they are underlined in the subjects symptomatic seventeen proteins. Among these particularly the cistatine C and the beta 2 microglobulinas, already

connected to Alzheimer's disease. The test had succeeded in confirming nine patients on ten, the initial diagnosis. Now the next footstep and to be able to also find the protein in the blood so that to make the easiest test.

2.7.1 Anamnesis

The anamnesis is the first footstep to try to diagnose the illness of Alzheimer, he proceeds with to word three types of anamnesis, family, remote and recent, so that to have a personal patient history and to try to understand if the disease is present or less. The family anamnesis consists of verifying neurological precedents, dementia or depressive in the family of the subject.

The remote anamnesis allows us to know the history of the patient, that is possible pathologies suffered in its life, in fact, it seems that the traumatized cranial have great possibilities to develop the illness. Besides remote analysis can be useful to understand if the patient in past has suffered from depression and therefore to be able to exclude both a case of pseudo depressive insanity.

While, the recent anamnesis analyzes the present of the patient, that is its symptoms and it questions the relatives of the patient to compare them.

Obviously the test is effected with a parent that can confirm that the patient declares the truth. If the patient succeeds in correctly bringing the remote pathologies, the recent symptoms, the examinations and the visits which has been submitted, he will slant for a picture demenziale.

2.7.2 Clinical exams

Over the anamnesis clinical examinations macaws also effected as the electroencephalogram, to verify possible alterations of the encephalic activity, examinations of the blood, to verify anemias or biochemists deficit, the examination of the cerebrospinal fluid, to verify the possibility of spinal

infections and TAC or magnetic resonance to observe possible anatomical alterations as expanded heart or cortical atrophy.

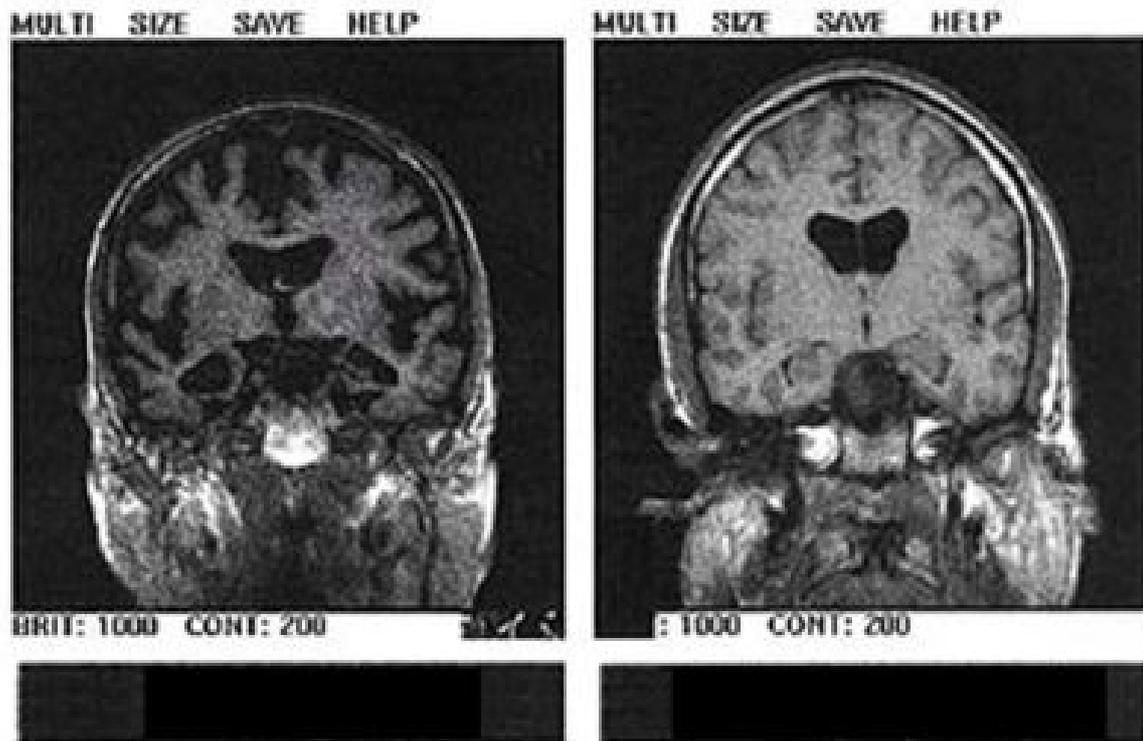


Fig. 7: *Magnetic Resonance of a Healthy Subject and of a Ill Patient*

From some time he is hypothesizing the use of the magnetic resonance for the diagnosis of Alzheimer's disease in how much with such tool it could be effected decades before the clinical symptoms are introduced.

The magnetic resonance is able to visualize the brain with great precision. Also losses of cerebral substance of the dimensions of match's head be underlined by the examination. The problem however that actually to now has prevented from using this technique to help in the diagnosis resides in the extreme variability of the cerebral structure among different people. The magnetic resonance could foretell the to rise up some Alzheimer's dementia with a 90% precision.

2. 7.3 Neuropsychological and cognitive evaluation

Besides they are effected a series of test for the neuropsychologic and cognitive evaluation of the patient, in which the picture is measured cognitive and the status of the principal cognitive functions.

The first administered test is, usually, the Mini Mental State Examination (MMSE), a test that in few minutes can give important information on the functions cognitive of the subject. Through the MMSE is possible to appraise the spatial orientation and storm of the patient, the cognitive level, the prassic functions, mnestic and graphics; then this test is an important point of departure.

The screening neuropsychologic uses of many tests that appraise different functions: breve memory term, for instance if the patient remembers some figures, of the words or of the sentences, memory for a long time term, ascertaining both the voluntary memory is the accidental memory, attentive functions, records functions, perceptive and prassic functions, and general cognitive functions. The presence of spatial-temporal disorientation, of deficit of memory, of acalculia, of anomy or agnosy (above all for animate objects), it makes the compatible clinical picture with the diagnosis of dementia type Alzheimer.

2.7.4 Differential diagnosis

Anamnesis and neuropsychologic evaluation furnish overall the rather precise diagnostic information. We must be remembered nevertheless that the only certain diagnosis can be had only post-mortem through the autopsy. It is therefore important, in the formulation of the diagnostic hypothesis, to appraise the possibility that the patient is affection from different pathological forms that introduce symptoms partly similar.

Among these we remember: alcoholism, or better alcoholic insanity, cerebral-vascular troubles, thyroid or cardiac (multi-heart attacks dementia), malnutrition, drug's reaction, cranial trauma or traumatic dementia, visual or auditory deficit, tumors or insanity tumoral, viral insanity from AIDS (AIDS Demential Complex), insanity from Parkinson's disease or insanity from Huntington's Chorea.

2.7.5 Future

With a blood analysis can be foreseen with years of advance if the Alzheimer's disease will strike. According to a study, conducted by the researchers of the Washington University School of Medicines, it's a protein the principal person responsible of the dementia development.

During the American search, whose results have been published on Science, the researchers, using changed mice, they have measured with precision the quantity of this protein in the brain, using the survey of the presence of the same one in the blood, thanks to a particular called chemical substance m266. Such substance results able to extract the protein from the brain and from the surrounding areas so that the levels of the protein in the blood they precisely resulted correlated to those of the present plates in the brain of the mice. In this way the man too can know with wide advance the to be disease revealed and before the mental decline. In more could be important because so could be avoided to confuse the Alzheimer with other types of dementias.

Besides the doct. William Klunk of the University of Pittsburgh Medical Center has isolated a substance able to cross the brain and to individualize the amyloid plates. This marker or the thioflavin-T, are in partnership to a radioactive indicator that underlines the amyloid plates of the brain.

3. The Alzheimer's disease therapy

The Alzheimer's disease is a progressive pathology, still incurable. A therapy that hands to the regression of the Alzheimer's disease doesn't exist, but there is only a symptomatic therapy finalized to temporarily take care of the cognitive symptoms and behavioral, and to guarantee to the patient a quality of the good life or dignified.

In halves the years 70 the scientists had exceptionally discovered some low levels of acetylcholine in the sick of Alzheimer, the acetilcolina is a very important neurotransmitter in the process of formation and memoirs' maintenance. Today, these studies and the following ones have brought the FDA (Food and Drug Administration) to approve in the United States five drugs for the symptomatic treatment of Alzheimer with light or moderate symptoms.

The first one, the tacrina, has been replaced by now by three new medicines, the donezepil, the rivastigmina and the galantamina, that act or stopping the acetilcolinesterasis enzymes involved in the destruction of the acetilcolina. The fifth one, the memantidina, is used in the treatment of the moderately serious and serious forms of some diseases and it acts stopping the receptors for the glutamate, another neurotransmitter that develops an important role in the processes of learning and memory. Unfortunately, to today, a definitive care doesn't exist for Alzheimer's disease. All the available medicines are only able to slow down the elapsed one of it and therefore to allow the sick to preserve for a longer time the (for months or a few years) functions cognitive.

According to the symptoms they are available different medicines: the acetylcolinesterasi inhibitors increase the levels of the neurotransmitter acetylcholine improving so the transmission of the nervous impulse; the antioxidants are used for slow down the dementia; the antidepressants are used in the treatment of the depression; the neuroleptics in the treatment of delirium and psychosis;

the carbamazepina, for the control of the aggressiveness and the nervousness; sedatives and adoption of measures palliative (to reduce the time of the afternoon rest, reduction of the departed time in the bed and to the exposure to the dazzling light during the hours of the day) for the therapy of the sleep's troubles.

As already said in the precedent chapter there is some tests to quantify the damage neurodegenerative caused by the Alzheimer's disease. These tests are useful, besides, to underline the presence of due improvements to the assumption of medicines anti-dementia.

I have already mentioned to the MMSE (Mini Mental State Examination), test that appraises the abilities cognitive, of orientation and of memory; it verifies the state of the disease. The MMSE represents an express and sensitive tool for the exploration of the cognitive function and of modifications in the time, applicable also in serious forms of deterioration. The administration asks for 10-15 minutes.

The total score, given by the sum of the scores that the patient has gotten to every items, can go from a minimum of 0 (maximum cognitive deficit) to a maximum of 30 (any cognitive deficits). The score is accustomed to it is not 23-24 and the greatest part of the insane elderly people it rarely gets scores of under the 24.

The SIB (The Severe Impairment Battery) is another test already used in subjects with functions too compromised cognitive for the classical tests, in fact, it tool for the therapists in the case of patients with severe degree of dementia. The SIB tries to fill the void left by other tools, furnishing the opportunity to get based data on the direct performance in an ample variety of assignments of low level, that keeps in mind of different cognitive troubles and behavioral specific, in partnership to insanity of severe degree. The greatest part of the tools of evaluation of the cognitive state assigns a score that reflects a general level of gravity.

Even if this can be very useful, a more objective evaluation of the relative trouble in different areas cognitive, as that furnished by the SIB, increases the knowledge of illness' process and it furnishes great clinical information in comparison to the advanced stadiums of insanity. The SIB appraises ability cognitive of low level. And' draws keeping in mind of the specific cognitive troubles and behavioral associates to insanity of severe degree. And' brief, it approximately asks for 20 minutes for the administration. And' compote of very simple commands that they are introduced with suggestions and it allows answers not records and partially correct. The SIB is a reliable tool and allows repeated evaluations.

The MODA (Milan Overall Dementia Assessment) is a brief battery that foresees the harvest is of data of investigation (drawn by a joined) that of data testistici that refers to manifold cognitive dominoes (attention, intelligence, memory, language, spatial knowledge and visual perception).

The check MODA concerns above all subjects affections from a dementia to the debut, even if it can also be applied to serious patient, for the more to thin physician-legal or of selection for a casuistry of study. The part to investigation articulates on a maximum of 35 points for the orientations (personal, storm, spatial, family) and in 15 concerning points the autonomy (primarily motor) in the life of every day. The general score is equal to 100. The carrying out of the whole check has lasted since 20 to the 30 minutes.

The ADAS-Cog (Alzheimer Disease Assessment Staircases, Cognitive Subscale) is a test that appraises the functions cognitive, particularly memory, language, orientation, attention and execution of simple assignments. The ADAS-Cog asks once for administration of 30-40 minutes. And' one of the tools used above all more for purposes of search.

The ADAS-Cog, in fact, was not born as a tool for the diagnosis, but for the characterization of the cognitive symptoms in Alzheimer's disease. The ADAS-Cog, preceded by a brief conversation

with the patient on you deduce neutral as the time, the patient's breakfast, etc., it consists of 12 fit tests to appraise the brief memory and middle term (words' re-evocation; words' recognition; learning of test's instructions); the temporal-spatial orientation; the language (oral ability, difficulty of denomination in the spontaneous language, understanding of the spoken language, denomination of objects and fingers, execution of commands); the prassia; the attention and the concentration. The scores of the ADAS-Cog go from 0, that absence its equal of error or deficit, to a maximum of 70, that points out a serious deficit instead in all the tests.

There is finally the CIBIC-Plus that is a test for the global clinical evaluation of the physician, after interview to the patient and the person that it assists him, on the behavior, on the cognitive functions and on the daily activities.

We now analyze all the drugs in commerce today for the treatment of Alzheimer's disease.

3.1 Acetylcolinesterasi's Inhibitors

The acetylcolinesterasi's inhibitors (Ach-EI): tacrina, donezepil, rivastigmina and galantamina, increase the central levels of acetylcoline that it compensates the cognitive deficits and it determines a temporary improvement of life's quality of the patient. They have a selective mechanism of action in to increase the colinergic functions, they show to induce only modest improvements but aren't nevertheless able to arrest the disease progress and their effectiveness decreases with to pathology progress.

The colinomimeticis indirect action inhibit the process of acetylcolina hydrolysis performed by the enzyme acetylcolinesterasi that, separating it in acetic acid and colina, hands to its inactivation.

Reducing the entity of the inactivation phenomenon, the acetylcolina persists in the intersynaptic spaces for a longer period in comparison to the norm, practicing so an action extended on the receptors with consequent expansion of the activity.

The acetilcolinesterasi is an enzyme omo-dimeric characterized by the presence of a site of bond for the cationic head of acetylcolina and a catalytic site from it's catalyzed the hydrolysis. This last is composed from the so-called catalytic (his440, ser200, glu327) triad that, before the interaction with the substratum, sees the formation of a hydrogen's bond among a istidine's imidazolic nitrogen and serine's hydrogen. Such interaction polarizes the bond hydrogen - oxygen of the same serina with the purpose to make the atom of more susceptible oxygen to form a bond with the carbonilic carbon of acetylcolina and to surrender the hydrogen. With an orchestrated mechanism, the hydrogen of the serine is surrendered to the oxygen of the colina with contemporary breakup of the estereric bond colina - acetate and formation of the acetate bond - serina. Subsequently it intervenes the water, that, thanks to her nucleophile priorities, idrolized the acetate bond - serina, bringing the enzyme to the situation of departure and freeing a molecule of acetic acid. The release of the colina from the site of bond happens for reduction of the affinity with the enzyme and for from another molecule of substratum.

There are few side effects to the use of the acetylcolinesterasi's inhibitors.

The acetylcolinesterasi's inhibitors must have employed with caution in the patients that have a precedent allergy history or adverse reaction to precedents treatments with the acetylcolinesterasi's inhibitors, a serious liver illness, a preexisting bradycardia, an peptic ulcer, alcoholism, asthma or obstructive chronic broncopneumopathy. The most common not desired effects produced by these inhibitors are: nausea, vomit, diarrhea and anorexia. The gastro-enteric not desired effects can be

minimized through a gradual increase of the dosing, the administration with the food, a suitable hydration and eventually with the employment (to limit) of an anti-emetic.

And' is shown that the symptoms of the disease of Alzheimer are in partnership to a deficit of the colinergic function to level celebrate her and therefore the employment of acetylcolinesterasi's inhibitors (AChE) is today still considered the more promising pharmacological approach in the symptomatic therapy of this illness.

3.1.1. Tacrina

The tacrina has been the first specific agent for the treatment of the Alzheimer's cognitive symptoms. Its employment in the Alzheimer's disease results limited, since the beginning of its marketing. In fact, besides the collateral effects of colinergic type, as it nauseates, vomit, bradycardia, etc, the tacrina is able to directly induce lesions at liver cells.

Its administration provokes in the 30% of the patients an elevation of the level of the liver enzymes type reversing and no symptomatic; in a 5-10% of the patients the elevation is more marked and such to be asked for a suspension of the therapy.

Because of the unfavorable relationship risk / benefit, the tacrina has never been recorded in Italy and, following the availability of other similar medicines, it has assumed a marginal role in the pharmacological treatment of the Alzheimer's disease.

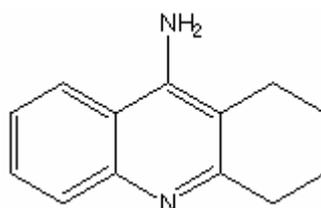


Fig. 8: Tacrina

3.1.2 Donepezil

The Donepezil (IUPAC name: 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one), active principle of two medicines prescribed that is commonly for the Alzheimer's disease the memac and the aricpet, has been approved in 1996 in the United States and in 1997 in Italy for the use in the Alzheimer's disease. A reversing acetylcholinesterasi inhibitor used for increasing the concentrations of acetilcolina to level of the cerebral cortex.

This drug has a bio-availability by oral administration of 100% and easily it overcomes the barrier blood-encephalic. It has a long half-life (around seventy hours), in fact, it allows an alone daily administration of the drug.

The donepezil has been experimented on patient with Alzheimer of light-moderate degree for a period of twenty-four weeks at the most, to the dosing of 5 or 10 mgs.

Modest improvements in the neuropsychologic tests (ADAS-Cog and CIBIC-plus) is gotten above all with dosing of 10 mgs / die, that is with the most elevated dosing.

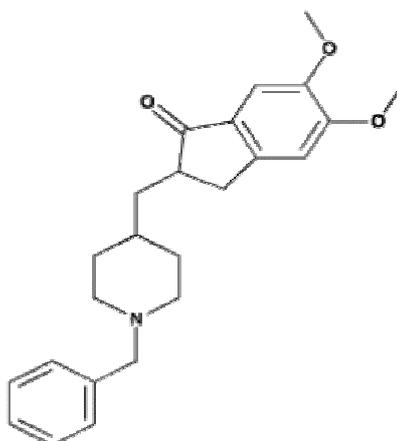


Fig. 9: *Donepezil*

The Committee of the NICE (National Institute for Health and Clinical Excellence) has analyzed 13 checked clinical random studies published and 1 not published, that have employed the drug anti-cholinesterasic Donepezil (Aricept).

Six studies have statistically shown a meaningful improvement some cognitive function after treatment with Donepezil in comparison to the placebo, valued through the staircase ADAS-Cog. Taller dosing of Donepezil were in partnership to an increase of the benefit.

Eight clinical studies have shown a trend toward the improvement of the scores MMSE after treatment with Donepezil in comparison to the placebo.

Seven clinical studies have appraised the effect of the Donepezil in comparison to the placebo respect to the global consequence through the employment of the staircases CGIC or CIBIC-plus. And' observes a great improvement, statistically meaningful, in comparison to the basal one in the scores CGIC or CIBIC - plus after treatment with Donepezil in comparison to the placebo.

You study that have brought the effects of the Donepezil on the functional results in the patients with Alzheimer's disease have underlined an improvement or a smaller deterioration, in the functional abilities, in comparison to the placebo. Nevertheless, these effects statistically are not meaningful results, in fact, the donepezil is not advantageous on the plan cost / effectiveness and offers least benefits.

The donepezil not desired effects mostly found are the diarrhea (in 12% of the cases) and the nausea (in 5% of the cases).

3.1.3 Rivastigmina

The Rivastigmina (Exelon) is an inhibitor unlike the tacrina and donepezil, pseudo-reversing of the suitable acetylcholinesterasi in the symptomatic treatment of Alzheimer's disease of light degree and moderately serious and in the illness of light and moderately serious Parkinson.

The medicine if precociously administered can help the patients to maintain for a longer time an enough autonomy's degree. The Rivastigmina effectiveness is confirmed by different clinical studies. Among these the Adena (Alzheimer Disease ENA 713) study that has involved 3300 patients for a period of 3 year-old observation, has underlined positive effects of the medicine on the cognitive troubles behavioral, on the incapability to develop the normal activities of the daily life at the same time the disease progression. The rivastigmina is seemed effective especially in patient that show a disease aggressive elapsed as those in juvenile age or with depressive or hallucinogenic crisis. It seems that the presence of hallucinations in the sick of Alzheimer or Parkinson patients treated with rivastigmina is an important input for the effectiveness of the drug. From a metanalysis (rivastigmina vs placebo) it notices him in the essays: middle difference in the ADAS-Cog (smaller or equal to 2.1), difference in the Progressive Disability Scale (of 2.2 points), CIBIC-plus improved in 7% of the patients.

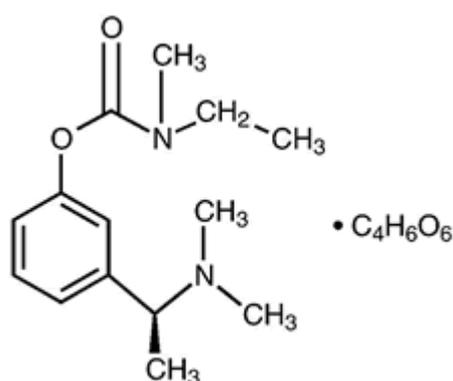


Fig. 10: Rivastigmina

The rivastigmina has been studied in the patients with Alzheimer's disease of light-moderate degree, to low (from 1 to 4 mgs) dosing and taller (from 6 to 12 mgs) dosing. The best results are gotten with the elevated dosing, to which it's in partnership however a great incidence of adverse effects, above all nausea and vomit, and in some cases the loss of the 7% of the bodily weight.

The rivastigmina's collateral effects is mostly at gastro-intestinal level seem to be due to the butilcolinesterasi inhibition, that would seem to increase the drug effectiveness in the most advanced phases of the disease but it would increase the not desired effects at GI level.

3.1.4 Galantamina

The galantamina (Reminyl) is a reversing cerebral acetylcolinesterasi's inhibitor and besides would also act on the presynaptic nicotinic receptors strengthening the release of acetilcolina from neurons. Galantamina is drawn out from the bulbs of *Narcissus pseudonarcissus*, it has a bio-availability for the 90% oral administration and an half-life of about 7 hours within the therapeutic (8-32 mgs die) dosing.

And' mainly metabolized to liver level by the P450 cytochrome and excrete with the urines. For this a particular precaution recommends to dose drug in patient with liver or renal insufficiency also of moderate degree.

They are three the principals studies checked random vs placebo that show the effectiveness of this drug on the cognitive symptoms in the initial phase of the illness of Alzheimer. The first two (USA-1 and USA-10) have been conducted in the United States, while the bystander has involved 86 specialistic centers in Europe and Canada.

The inclusion criterions are a history of cognitive progressive decline in the last six months, a probable diagnosis of Alzheimer, a score to the Mini Mental State Examination between 10 and 11

and a score to the equal ADAS-Cog at least to 18. In everybody and three the studies the subjective feeling of effectiveness of the medicine has also been appraised from the caregiver through a correct corroborated staircase. Every study has involved around 600 patients for a varying period from four to six months. USA-10 has applied a model for which the patients have been distributed in four arms (placebo or galantamina to the dose of 8, 16 or 24 mgs die). The final dosing has been gotten with increases of 8 mgs the month. USA-1 and the international study, reaches instead, according to the random arms, final doses of 24 or 32 mgs with progressive increases of 8 mgs the week.

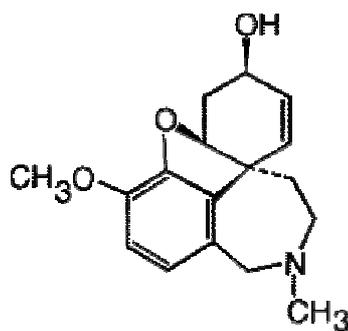


Fig. 11: *Galantamina*

The conclusion, fortified by a recent revision, it's that the treated group preserves a performance to the cognitive tests unchanged in the first six months of care in comparison to the group treated with placebo, that records a middle worsening of around six points to the ADAS-Cog.

Besides the medicine would slow down the appearance of the psychiatric and behavioral symptoms. Statistically the meaningful results are gotten with doses than at least 16 mgs die, and they are directly proportional to the increase of the dosing up to 32 mgs. You advises to begin the treatment with 8 mgs die increasing up to 16-24 mgs two daily administrations.

The no desired effects are above all to load of the gastro-enteric apparatus, as it nauseate, vomit and diarrhea. In some cases dizziness, anorexia and rare syncopations due to the deceleration's action of on the cardiac management are also manifested. The gastric symptoms can be appeased assuming the medicine during the morning and the evening meals and with a suitable liquids introducing. In some cases of particular sensibility can be useful the concomitant assumption of a antiemetic medicine.

A study of the one year-old duration, finished in Great Britain, has shown that the Galantamina (Reminyl) is superior to the Donepezil (Aricept) in the treatment of the Alzheimer's disease. The Galantamina has improved in meaningful way the choice reaction time (CRT) in comparison to the Donepezil, after only 6 weeks of treatment.

The improvements in the ability to maintain the attention after assumption of Galantamina seem due to its action on the nicotinic receptors. In fact, the Galantamina increases the levels of the acetylcolina through two mechanisms, the one inhibiting the acetylcolinesterasi, the other one favoring the activity of the nicotinic receptors. The nicotinic receptors develop an important role in the maintenance of the attention and the concentration. Besides the patients essays with the Galantamina have a great probability, in comparison to those essays with the Donepezil, to improve or to maintain unchanged the really state of dementia. To the thirteenth one and the twenty six week, the score MMSE (Mini Mental State Examination) among the patients essays with the Galantamina has introduced an improvement in comparison to the basal one, with a return to the basal values to the fifty two week. In the patients essays with the Donepezil, an improvement of the score alone MMSE a thirteenth week has been noticed instead. To the twenty six week the score MMSE is returned to the basal values, with a worsening to the fifty two week¹¹.

¹¹ 6th Congress of the European Federation of Neurological Societies, Vienna 2002

3.1.5 Last discoveries

The ganstigmina (CHF 2819) and' an inhibiting ounces daily of the acetylcolinesterasi, in clinical development-Phase II, for the treatment of Alzheimer's disease. This molecule and' a powerful person and selective acetylcolinesterasi's inhibitor: in vitro it shows a selectivity one hundred and five turned great for the acetilcolinesterasi that for the butyrrilcolinesterasi. Besides and' is shown a selectivity drug-dynamic to central (inhibition ten times great of the central acetilcolinesterasi in comparison to the peripheral one) level.

A animals study model of Alzheimer's disease have shown a dose-dependent attenuation of the cognitive deficit with oral ganstigmina in different experimental paradigms. Studies of microdialysis "in vivo" have shown that ganstigmina induces a meaningful increase of extracellular serotonin concentrations over that of acetylcolinesterasi. The stimulate effect on the central serotonergic functions could represent a therapeutic potential for the patients in which the cognitive deficit and' accompanied by a depressive syndrome.

The new data suggest for a long time a potential protective effect of the treatment term with ganstigmina in Alzheimer's patients since this molecule stimulates the release of the soluble form not amyloid similar of the amyloid's precursory protein in the cells of human neuronal-crab. Currently the clinical development of ganstigmina and' in progress in USA and Europe.

Together with the ganstigmina, another carbammic inhibitor is the N1, N8-bisnorcimserina and both interact with the active site through the carbammic group.

There are finally two reversing acetylcolinesterasi inhibitors that seem to be useful in the therapy of Alzheimer's dementia and they are SPH1371 and SPH1373.

3.1.6 Conclusions

The effectiveness, even if modest, shown by the anticholinergic agents in the therapy is reproducible only in the clinical practice in presence of determined factors:

1. Sees the specificity of these medicines a diagnosis of Alzheimer's disease is necessary, from at least six months, with exclusion of other causes of senile dementia (above all vascular causes), not to uselessly expose the patients to non appropriate therapies.
2. Once effected the diagnosis of Alzheimer's disease, must be appraised that is in a precocious phase and that is of light-moderate degree, since the effectiveness of these cholinergic drugs has only been made a will in this circle. To the purpose to notice the light-moderate disease's degree is opportune at least to submit the patients to the MMSE test. A score among 10 and 24 is indicative of light-moderate Alzheimer. To confirmation of cognitive functions state of the patient, would be opportune to administer a further test besides, as for instance the ADAS-Cog.
3. In the choice of the medicine, since studies of comparison don't exist, it would be owed at least account of the exclusion criterions of patients in the effected clinical studies. For the donepezil they have been: diabetes insulin-dependent or other endocrine disorders, asthma, pulmonary obstructive troubles, troubles to load of the gastro-intestinal or cardiovascular line, hypersensitivity verified towards the cholinesterasi inhibitors, anticholinergic drugs assumption, anti-spasms, antidepressants and antipsychotics. During the experimentation, also other active medicines on the

SNC had been abolished or limited in the use¹². For the rivastigmina, in the studies of phase III, all the patients have been excluded with serious disease in progression and patients with indicative clinical data of the liver and renal deficit functionality. In the studies checked of phase III have been included patient however with concomitant pathologies as the hypertension. The administration of medicines that could influence the determination of the effectiveness has been forbidden, to exception of the hydrated “cloralio” in case of insomnia or occasional nervousness¹³. It’s worth stop on these restrictive criterions, above all as it regards in donepezil. If from a side it’s correct that restrictive criterions are used, for the correct carrying out of the checked clinical study, from the other one it needs to consider that is rather rare, in the clinical practice, to meet patient in advanced age without pathologies or concomitant treatments.

4. Should be considered the possibility to administer the colinergic drugs dosing more elevated, if born, since her totality of the clinical studies has almost shown a good effectiveness in to improve the cognitive troubles proper to the most elevated doses.
5. A precocious monitoring of drugs bearly must be effected, since above all to tall doses the onset of collateral effects is had, such to ask for the suspension of the treatment. A first evaluation after two weeks of therapy can be made for verifying the appearance of collateral effects. The more communes both for the donepezil and for the rivastigmina are nausea, vomit and diarrhea. For the donepezil has been in relief insomnia, while for the rivastigmina anorexia. Particularly the rivastigmina has an

¹² Birks, Melzer- Donepezil for mild and moderate Alzheimer’s disease - 1999

¹³ Rivastigmine, European Public Assessment Report (EPAR), CPMP/243198 rev. 1

elevated incidence of collateral effects, above all to tall doses, so much to be recorded percentages of abandonment of the studies around 30%.

6. If the drug is bear, must be perform some evaluations of the patient's answer to brief and for a long time term, the first one should be effected to three months and the second to six months of therapy, again submitting the patient to the cognitive tests.
7. It is opportune to interrupt the treatment if there are problems of tolerance and compliance, if a cognitive deterioration is recorded to the levels of pre-treatment or, straight, if is assisted to a worsening. The treatment can be maintained instead if an improvement or a stabilization is verified or also a deceleration of the disease progression.
8. It is important to hold under observation the patients besides, when they suspend the therapy, since cases of precipitous worsening of the insanity are brought. If this is verified in an observation's arc of six weeks, following suspension of the pharmacological therapy, could be opportune to take back the treatment.

Considering that the greatest part of the studies till now effected has considered periods around the six months, the easiest strategy to cross it seems the evaluation of the patient cognitive state to regular intervals, deciding as soon as whether to continue or no the therapy. From how much said is understood as the correct use of such drugs implicates a diagnostic-therapeutic run anything else other than simple. In this motivation probably resides for which their prescription is reserved, according to the immission's decree in commerce, to the "experienced experts in the management of Alzheimer's disease."

3.2 Memantina

The memantina is a low affinity antagonist of the N-metil-D-aspartato (NMDA) receptors and acts on the glutamate's transmission; it's also authorized in Italy for moderate to serious Alzheimer's disease treatment. The memantina has been approved from the Food and Drug Administration for the treatment of the Alzheimer's disease in moderate-severe phase, and the founder of a new drugs' class represents for the treatment of this neurodegenerative pathology.

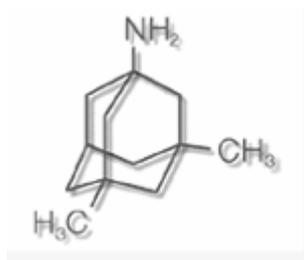


Fig. 12: *Memantina*

You believes that the on-excitement of NMDA receptors practiced by the glutamate, a neurotransmitter, both at the base of the Alzheimer's disease. The glutamate develops in fact an important role in the processes of memory and learning. The excitotoxicity produced by elevated levels of glutamate is held in fact to be responsible of the neurons alterations and the possible cellular death observed in the Alzheimer. And' hypothesizes that the memantina stops in selective way the effects of the excitotoxicity of the glutamate. And' a completely different mechanism of action from that of the actual treatments for the Alzheimer as the acting anti-cholinesterasics. Evidence of a role of the excitatory activity of the L-glutamate exists in the Alzheimer's disease pathogenesis. An antagonist to low affinity of the receptors NMDA (N-Mhetyl-D-Aspartate) as the memantina (Axura / Ebixa / Namenda), can prevent the neurotoxicity of the excitatory amino acid without interfering with the physiological actions of the glutamate, applications for the memory and the learning.

A study that has involved 252 patients with moderate-severe form of Alzheimer's disease has shown twice after six months of treatment with memantina in dose of 10 mgs to the day, a meaningful improvement in the cognitive function and in the daily activities, and in general of the clinical picture. Besides a reduction of the assistance's necessity has been observed towards the patient. The memantina doesn't is not result in partnership to a meaningful incidence of adverse events.

The memantina must be uses with a lot of precaution the patients with epileptic crisis and in the subjects with a recent heart attack or that they suffer of cardiac insufficiency or of hypertension not checked. And' necessary monitoring the renal functionality in the patients with moderate renal insufficiency adapting the memantina's dosing. For this motive, the employment of this mixture is dissuaded the patients with serious renal insufficiency.

Must be avoids the concomitant administration of the memantina with the amantadina, the ketamina, the destrometorfano and other NMDA antagonists. And' unadvisable the assumption of the memantina in pregnancy and the women that assume memantina should not nurse.

The no desired effects observed during the treatment with memantina are light or moderate. No desired effects non common are: anxiety, up-tone, vomit, bladder's infections and libido's increase. In the subjects with history of epileptic attacks, the memantina can facilitate the onset of epileptic crisis. In general, the adverse reactions more communes, with an incidence under 2% are: hallucinations, confusion, dizziness, cephalaea and exhaustion. The Memantina has not caused a meaningful number of no desired effects. Rather they are more frequent results in the placebo group. The most common collateral effects brought in both the groups have been: nervousness, urinary incontinence, urinary streets' infections, insomnia and diarrhea.

The data in the patients with vascular insanity, light-moderate, points out a beneficent Memantina's effect to the dosing of 20 mgs / die on the function cognitive measured to the twenty octave week.

According to the auditors of the Cochrane, the Memantina 20 mg / die is able to produce a meaningful reduction of the deterioration within 28 weeks in the patients with Alzheimer's disease, moderate-serious. The Memantina effect in the patients with Alzheimer's dementia, light-moderate it is not known. The patients with light-moderate form of vascular insanity, that has received the Memantina 20 mgs / die, have introduced a smaller cognitive deterioration to 28 weeks, but the clinical effects are not so evident results. The medicine results well born and the incidence of no desired effects has been low.

3.3 The C kinasi protein role

New drugs defined activators of the C kinasi protein (PKC) seem to succeed in attaching to the root the Alzheimer's disease striking the causes of it over that the symptoms. It is how much it results from test conducted on the mice. Many scientists affirm that it would currently deal ahead with a footstep in comparison to the medicines in use for the therapy of Alzheimer's disease. In the study, of which it gives account the medical magazine Proceedings of the National Academy of Sciences, the team driven by Alkon has appraised the effects of two activators of the PKC, benzolactam and briostatina, in cellular crops and in sick mice of Alzheimer. In the crops the medicines have induced some changes that would seem important to prevent the neurodegenerative damage of this pathology. In the mice, they have reduced the accumulation of the protein instead responsible of the damage or the protein, beta-amyloid. They have, therefore, contributed to prevent the premature death and to improve the behavioral profile.

The briostatina is currently in study as no tumor agent in the human beings, but sees its low toxicity it could be employed as drug in the therapy of the Alzheimer's disease being a protein that facilitates the necessary substances' synthesis to the cerebral nets. In fact it would have as therapeutic target that to consolidate the memory in the patients with manifested Alzheimer.

3.4 AF267B

The molecule, called AF267B, is effective against the Alzheimer. The researchers of the University of Irvine, in California (among which two Italians, Antonella Cacciamo and Savior Oddo) and of the Israeli institute of biological Searches have studied the therapeutic effects of a M1 agonist drug, the AF267B note, that stimulates an enzyme that inhibits the beta-amyloid plates production.

The medicine, experimented on trans-gene mice sick, it mimes the effects of the acetylcolina, the neurotransmitter essential for memory and learning, that it ties him to the receptors M1 of the brain's cells. Unlike the other medicines M1-agonists, already used for compensating the progressive diminution of the natural neurotransmitter in the patients, and to compensate the progressive diminution of acetilcolina in the Alzheimer's disease AF267B also stimulates in the neurons the production of the enzyme alpha-segretasi, that the precursor of the protein that separates beta-amyloid, preventing the production of it.

If the results gotten by the animal model will also be gotten in the man, the new molecule will constitute ahead an enormous footstep in the struggle to this disease, also because the mixture is able to overcome the barrier blood-encephalic and can easily be administered by oral or parenteral.

3.5 The sage

The Chinese natural remedy, the miltiorrhiza sage, known also as "danshen", it seems to be a good support for the health cardiovascular, since rich of heart protective fitochemical (how sour salvianolics) and antioxidants.



Salvia miltiorrhiza

Fig. 13: *Salvia Miltiorrhiza*

In effects, according to a relationship, the sage "it has revolutionized the management of angina, heart attack and ictus in the Chinese society." The greatest part of the searches on the sage have put in evidence ownerships of protection, particularly in the cases of angina (a condition in which insufficient of oxygen is available for the same cardiac muscle), heart attack and ictus. The sage dilates the arteries and blood vases increasing the flow of blood. This is very meaningful, because the heart attacks are caused by blood plaques that admit and the form of clots. A heart attack is verified when one of the coronary arteries seriously become or totally jammed, usually from a clot of blood. While it is being, the sage, is mainly studied for its potential role in the prevention and in the treatment of cardiovascular illnesses, a recent search has shown other important benefits for the health from this plant. The powerful antioxidants and fitochemical in the sage have been studied for their effect on the loss of bony tissue caused by

estrogens deficit in the animals. Surprisingly, the sage prevents completely the loss of bony tissue.

In the case of health of the brain, the miltiorrhiza sage has shown to have an important protective effect against the amyloid protein that develops a central role in the Alzheimer's disease. Main point is to know that the sage succeeds in preventing the accumulation of the amyloid protein in the brain, therefore to avoid that the neurofibrils skeins are formed, and, besides it reduces the neurodegenerative damage caused by the same amyloid protein in the patients struck by Alzheimer's dementia¹⁴. The new searches are directed to use the sage in the Alzheimer's disease, or better the essential oil that is drawn by its leaves, in this way to try to embank the damages caused by the due neuronal degeneration to this weakening pathology.

3.6 Ginkgo Biloba

The Ginkgo biloba is a belonging plant to the family of the Ginkgoaceae, it was considered sacred in the East and, according to some, it has a secular employment in the Chinese traditional Medicine. This plant contains many mixtures endowed with pharmacological activity, identified in the leaves from which the dry extract is drawn, are mainly: terpens (they are of particular interest some diterpens individualized with the name of Ginkgolidis A, B, C, M, J and of the Bilobalidis); poliphenols (above all glicosids flavonoics derived of the Oakol, of the Campferol and of the Isoramnetol and some bio flavonoids among which the Ginkgetol); other individualized components are composed aliphatics, phenolics and organic acids.

¹⁴ MK Tang, Zhang JT, Salvianolic acid B fibril inhibit formation and neurotoxicity of protein beta-amyloid "in vitro", *Acta Pharmacol Sin.* 2001



Fig. 14: *Ginkgo biloba*

The numerous effected studies and biological experimentation have, in following phases, shown, with reference to the therapy of the dementias, the followings pharmacological actions:

- the flavonoids have multilevel action of the circulatory system with vase-dilating activity, for action on the smooth average's muscular fibrocells, diminution of the capillary permeability and increase of the venous tone. On some types of cerebral edemas and retinic experimental and on models of ipossia post-ischemic has been shown an increase of the cerebral bedewing with increase of the glucose's concentrations and ATP in the nervous tissue with inattivaction of the toxic radicals of the oxygen;

- the terpens, and particularly the ginkgolide B, are endowed with specific action PAF-acether's antagonist, phospholipidic intercellular mediator implicated in the plaques aggregation, in the trombogenesis and in the processes of aterogenesis. To the bilobalide, as also to the ginkgolidis A and B, a specific action neuronal protective has been recognized. The studies of pharmakinetics, conducted on animals and subsequently on the man, based on observation and measurement, after administration of marked extract radioactively they have shown, that the bio availability results to be of 98-100% for the ginkgolide A, of 79-93% for the ginkgolide B and at least of 70% for the bilobalide.

The studies of toxicology have, until now nearly shown a total absence of chronic toxicity not individualizing some biological and histological change in the rapeseeds after prolonged administration (doses from 30 to 60 mgs / kg / die). Also acute toxicity can be considered extremely modest being established the DL50, for the mice of around 7 gr / kg for oral administration and of 1,5 gr / kg for by intravenous, to an elevated value clearly in comparison to the therapeutic dosing.

Seem me correct to remember, first of all, some therapeutic indications, different from those in matter, that a lot of simply is: acufeni and dizziness of vascular and regressive origin, some pathologies bronchuses-spastic, some circulatory pathologies among which the Claudicatio intermittens, the venous insufficiencies, the phlebitis and the hemorrhoids.

In specific reference to the demential syndromes, the scientific literature in the last decades has proposed a series of random studies, or in double blind, that show the effectiveness of the dry extract of leaves of Ginkgo biloba in the initial forms of Alzheimer's disease.

Particularly interesting they are the studies conducted between 1994 and 1997 that have underlined the necessity, essential for a serious and sure therapeutic use of dry leaves' extracts of Ginkgo biloba, to be able to prepare a fitotherapeutic prepared assembled, stabilized and standardized that they guarantee least concentrations of the 24% of flavoglicosids and the 6% of terpens (of which 3,1% of ginkgolids A, B, C). The daily doses of product employee they vary from 120 mgs / die to 240 mgs / die.

The patients have been valued with weekly or monthly periodicity in the studies more extended using different staircases of evaluation that, in the study of P. LeBars has been the ADAS-Cog (Alzheimer's Disease Assessment Staircases Cognitive), the GERRI (Geriatric Evaluation Relative's Rating Instrument) and the CGIC (Clinical Global Impression of Change). Such staircases of evaluation allow to objectify the cognitive performances, the primary and secondary functional

patients' abilities, is personal is social. All the studies arrange in to ascertain that, after the first month of treatment, substantial cognitive abilities' improvements are observed and of the attention's threshold, with parallel control, of the behavioral, or psychological alterations, what the motor iperkinesia, the anxious-depressive lines, etc.

The study of P. LeBars that, for 52 weeks, it has monitoring - to comparison with a group placebo - 309 patients, excluding solo patient insulin dependent, or with psychiatric pathologies, in multi-therapy, at the end of his job has handled to compare the scores gotten in the various evaluations, among group placebo and treated group, getting: 1,4 points in the ADAS-Cog, against 0,04 of the group placebo. Through a statistic elaboration he has affirmed that the patients essays with Ginkgo biloba has shown an improvement of the cognitive functions for six months in one year. The collateral effects underlined in these studies have been defined of modest entity, they have almost exclusively been to load of the gastro-enteric line and this has allowed the authors to define as sure the therapeutic use of Ginkgo biloba. This underlines us the possibility of intervention on the patients with dry extract of Ginkgo biloba departing from the consideration that around this matter there is a discreet "ferment" in the scientific world.

It needs, however, to make some considerations on the use and the consumption of the ginkgo as possible medicine for the Alzheimer's dementia. Essential condition for the use of the dry extract of Ginkgo biloba is the possibility to be able to have titled products, standardized and stabilized; this requisite is extensible to all the fitotherapic products that would be able and they would owe so to enter to belong to the usual prescriptive profile from the physicians.

There is obviously the necessity to individualize, for the treatment in object, patient in which insanity is in state of debut or, to the limit, in the first evolutionary phases, these patients must be monitoring with controls to brought closer frequency and the results objectified through staircases

of evaluation that in the common practice can confine to the Mini Mental Status and to a staircase of functions' evaluation of the residual autonomy, this last will be actually of help in the monitoring the patient for all through the pathology to the states of great compromised.

It needs to underline particularly the possibility to guarantee to the patient a best quality of life, also social and report, that for the time being it's the only objective to establish him when we approach a patient insane date the irreversibility of the pathology. Must be set more attention the collateral effects and the precautions to adopt him during the therapy. There is no reference to the fact that the Ginkgo biloba, interfering with the PAF-acether, must be uses with extreme caution in patient in concomitant treatment with anticoagulants drugs. Such situation, since in many cases can be an absolute side effect to the treatment, the physician sets in the condition to have to complete an analysis, around the possibility to undertake a concomitant therapy, to suspend the possible anti-admitting therapy for the mono-therapy with Ginkgo biloba, or to postpone to the therapeutic possibility. It seems opportune to remember that, after the reflections that the physician must complete with science and conscience, to have the informed consent is necessary from the patient; everything how much dictate him it notices to be, in the daily practice, a big "grate" of limitation in the selection around the number of patients that can be approached with this therapy. During the treatment with Ginkgo biloba can rise up other secondary no desired effects that, in the recent analyzed studies, are not mentioned, while they are being enough frequent in the practical activity and can find mention in other publications, appearance of nervousness and insomnia that, being generally caused by up-dosing, they ask for an posologic adjustment, cutaneous allergic reactions and cephalaea. Last consideration is that the treatment with Ginkgo biloba can also be extended for long periods, but its utility finds term when the mental deterioration of the insane patient reaches levels proper of the most advanced disease's phases, when it comes to miss the substratum of action

for the extract of Ginkgo biloba and the attention of the physician is moved toward other incoming neurological problems.

4. The Cronos project

The Cronos project has been an innovative model through which the Health's Office integrated the process of distribution and reimbursement with a observation study on wide staircase, using the net of own specialistic centers, in collaboration with the general medicine's physicians and the chemists, guaranteeing a relief continuity between hospital structures and territorial assistance.

The objective has been to improve, as far as possible, the Alzheimer's patients' quality of life and health. This is been able to realize through the introduction of a series of services innovative able to concretely help the patients and their relatives and with the supply of therapies that, somehow, can try to oppose the elapsed of the disease.

The Project foresees the free prescription of three recorded drugs at european level (Donepezil, Rivastigmina, Galantamina) for the treatment of the Alzheimer's disease in the light and moderate form, to which a observational study is accompanied on the plans of pharmacological treatment.

The Health's Office has completed its proposal to make prescribed by the National Sanitary System (NSS) the two acetylcolinesterasi's inhibitors (with D.M. of 20/07/2000) for Alzheimer's disease, the donepezil and the rivastigmina.

The project thing intends:

1. to sensitize the sanitary operators and the patients' families through the use of all the tools to disposition (devoted newsletter, average, internet) with the purpose to make to grow the social disease awareness and to improve the therapeutic and existential interventions;

2. to furnish the drugs free today available;
3. to guarantee a relief continuity between the specialistic structures and medicine of base.

The Cronos project, that has had beginning September 15 2000, has been conceived for making available two medicines maintaining low the burden to load of the NSS, and was born for having observational form of study.

4.1 How happened the project admission

The General Medicine physicians individualized patient admissible to the treatment on the base of a diagnostic suspect or the existing clinical documentation already, and they address them to one of the authorized centers (Unity of Evaluation for the plans' monitoring of pharmacological treatment for the Alzheimer's disease - UVA), that it effected or it confirmed the diagnosis and it established the degree of severity of it according to the MMSE: "they will entirely be admitted the patients to the treatment with light-moderate probable Alzheimer's disease."

The physicians must follow a monitoring's card divided in two phases:

- Phase 1: it visits initial near the physician of general medicine, before visit near the evaluation unity, adjustment therapy, evaluation and confirmation therapeutic plain.
- Phase 2: evaluation every t months.

The Regions and Autonomous Provinces had to furnish the list of the fit structures to the diagnosis and the treatment of the Alzheimer's dementia (AD) so that to guarantee the maximum accessibility to all the interested patients. All the identified structures were qualified as unity of evaluation for the plans' monitoring of treatment for Alzheimer's disease. The evaluation's unities had to be identify in the form of based functional unity on the coordination of the neurological

competences, psychiatric, insidestic and present geriatric within the hospital departments and the business specialistic services, of the general medicine and of the domiciliary assistance's services.

Could be suitable in the district the appropriate relief level for the necessary operational coordination between competences and remarkable services in comparison to the different aspects of the assistance to the patient with Alzheimer and to his relatives.

All the evaluation unities owed, however, to answer to the followings requisite:

- ability to appraise the subject with cognitive-behavioral troubles following a structured diagnostic run.
- ability to maintain a contact and a continuous interaction with the physician of family so that the continuity of the cares of the patient is guaranteed;
- structures availability for the antycholinesterasici's drugs disbursement for the symptomatic treatment of the Alzheimer's disease.
- I hock to respect the present monitoring protocol of the treatments.

The interested patients have been sent evaluations to the general medicine's physicians unities on the base of a diagnostic suspect or on the base of clinical documentation, already available, that makes to hold the eligible patient for the treatment. The general medicine's physician, having regular contacts with the elderly people and with their families, it's, in fact, in a favorable situation to recognize the precocious disease signs and to help the family ones in the relief management of the patient.

The principal diagnostic criterions to define a probable From are the followings:

a) Criteria that must contemporarily be present: established insanity with examinations and documented by objective test (for ex. MMSE), memory troubles and than at least another cognitive function (for ex. language or perception), progressive deterioration of the memory and than at least another cognitive function, any conscience's trouble, appeared among the 40 and 90 years, absence of other pathologies of the SNC or systemic diseases that can cause dementia.

b) Criteria to support of the diagnosis: the motor abilities compromised, the independence's reduction in the carrying out of the daily activities, family history of similar troubles, neuroimaging picture (for ex. cerebral atrophy).

4.2 Therapeutic program

In the eligible cases to the treatment with colinesterasis inhibitors, can be begun, to choice, with one of the two authorized medicines currently in Italy.

The medicines that are prescribed with the Cronos project are, Memac and Exelon.

The Memac, donezepil, is an "anti-dementia drug used for the symptomatic treatment of light moderate and degree Alzheimer's disease"¹⁵. The dosage is of 5 daily mgs in an only administration for by oral before sleeping, after one month of therapy the dose is increased to 10 mgs.

The Exelon, rivastigmina, drug is anticolinestarasic used for the "symptomatic treatment of the dementia type Alzheimer from light to moderately serious and the symptomatic treatment of the dementia from light to moderately serious in patient with idiopatic Parkinson' disease."¹⁶. The dosage is of twice for die (1.5 mgs).

¹⁵ Memac illustrative sheet

¹⁶ Exelon illustrative sheet

The manufacturing firms have stuck to the application of the Health's Office to directly furnish free the products (in wrappings opportunely countersigned) to the UVA for the first four months, later which the medicines will directly be available in the pharmacy, with to discount, for the NSS, on the 30% anticipated current price.

The treatment of the single patients will be monitoring at the respective Medicine General's physicians, that will guard the appearance of collateral effects or adverse reactions and they will appraise the clinical course of the patient; the UVAs, every time that the patient will be visited, they will complete a card, of which they will transmit copy to the residence's ASL of the assisted ones; the Health's Superior institute will acquire the dates of such cards from to representative champion of ASL, it will constitute an informative files and it will complete, within two years, to general relationship on population admitted to the treatment, use of the anticholinesterasic medicines, clinical dates, motives for cessation of the treatment, adverse reactions, missed compliance, etc.

The treatment will be interrupted in the houses of last tollerabilità or scarce compliance, when the score MMSE has reached an equal or inferior value to 10.

4.3 Scanning treatment

The whole the information necessary for the plans' monitoring of pharmacological treatment of the Alzheimer's disease, has been picked through two typologies of cards to compile edited by the evaluation unities: a card of beginning treatment that during of the therapeutic plan formulation and a card is compiled in the following visits that every time is compiled that the patient is visited near the unity.

The drugs' disbursement must follow the following scheme:

Phase A: the medicines are disbursed near the evaluation unities: visit for the patients admission to the treatment; to 1 month from the first visit; after 3 months from the first visit.

Phase B: the medicines are disbursed through the physician of general medicine's prescription: on the base of the therapeutic plan defined by the evaluation unities, the patients are regularly followed by the general medicine's physicians.

According to the quoted document of the CUF, the general program asks for an epidemiological overseeing of the anticholinesterasic's medicines use. To such end the evaluation unities will regularly send copy of the survey's cards of the data (monitoring and following visits) to the ASLs of patients' residence. The ASLs have provided to send every four months, to the Evaluation's Drugs Department and the Drug-vigilance of the Health's Office, a summary prospectus of the patients' number admitted to the treatment and of the patients' number that had interrupt the treatment. The Health's Superior institute has acquired the survey's cards of the data from a representative ASLs champion centralizing all the information in an only database. Has provided, therefore, to the analysis of such information to the purpose to produce a general relationship on the population admitted to the treatment, on the use of the anticholinesterasic medicines and on the motives for treatment cessation what for instance the missed benefit, the appearance of no desired effects, a missed compliance, etc. It foresees that such relationship can be made within two years available from the beginning of the monitoring.

4.4 Diagnostic process

This phase mainly concerned the General Medicine's Physician (GMP) that during an interview for a normal clinical control or on family indication ones of the patient, often the first ones to notice a behavior "strange", can set the disease's suspicion. The GMP has been helped, in to formulate the

dementia suspicion, from the administration of a evaluation's simple test of the mental functions what the Mini Mental State Examination (MMSE).

Was effected by the evaluation unity using a specific diagnostic run structured that it foresees:

- it anagraphic's files that also defines the social subject condition what the cohabitation in family, the civil state, etc., factors these that, especially in the elderly one, they have a great influence on the disease's expression;
- family anamnesis that underlines above all the presence of neurological and psychiatric pathologies;
- physiological anamnesis, whether to bring the factors that could have a role in the dementia expression what: level of education, menopause age, alcohol's consumption, etc.;
- pharmacological anamnesis whether to point out in detail type and drug quantity in use or recently used that could have influenced the state of the functions cognitive of the subject;
- pathological, both remote and next anamnesis, that allows to underline the possible presence of serious pathologies that can worsen the cognitive picture (respiratory insufficiency, cardiac troubles, diabetes, crisis ipo / hypertensive, etc.);
- general objective examination that must be particularly accurate and focused to define the presence of organic pathologies that can complicate the dementia picture and whose recognition and treatment represent a fundamental therapeutic dementia moment. Also the evaluation of the functional state cannot put aside from the recognition of all those pathological conditions that, adding to the disease, they reduce the level of self-sufficiency of the patient;

- neurological objective examination that also considers signs and symptoms that can address toward focal (vasculatity suspicious) deficit, as well as liberation signs (grasping, etc.) enriched of tools and useful staircases for the differential diagnosis among the different forms (ex. the Hachinski's Ischemic Score, for the differential diagnosis between the degenerative insanities and those vascular) ;

- psychometric and behavioral evaluation, based on the use of test that explore various cognitive areas (memory, temporal-spatial orientation, language, prassia, ideation and judgment, etc.), as well as the affective (anxiety, depression) state and the presence of behavioral and psychic troubles (hallucinations, deliriums, etc.); the neuropsychologic evaluation, to be fundamental in the diagnostic one among the various dementia's forms, allows further the survey of conditions characterized by deficit very cognitive light, what the "mild cognitive impairment" that could express benign pictures to scarce evolution of a real dementia;

- routine's hematological examinations and hemato-chemical as VESs also include, serum dosing of vitamin B 12 and folati, serumlogy for the lue, TSH, urines's examination;

- Chest Rx, ECG;

- neuroimaging's examinations (TC / RMN).

This diagnostic run, in the suspect of specific dementia pictures less frequent comparison, can be integrated from further investigations what:

- studies of flow and cerebral metabolism

- cerebrospinal liquor examination

- dynamic liqueur study

- EEG and PE
- prionic proteins' search
- serumlogy for HIV.

The differential diagnosis will be set particularly toward the following dementia's forms: vascular insanities or primary degenerative insanities. Within the primary degenerative insanities it needs to differentiate the Alzheimer's disease from the other neurological pathologies with dementia as the Parkinson's disease, the up-nuclear progressive paralysis and the cortex-basal degeneration, the bodies spread Lewy's disease, the Huntington's Chorea, the prions' illnesses, the Pick's disease, etc. This pertinence assignment of the evaluation unity that has adopted the clinical criterions recommended for the various forms.

4.5 Instruments for diagnosis

The first test that effects him is the Mini Mental State Examination (MMSE), as it happens in the normal Alzheimer's diagnosis. To follow there is an example of the test that is administered to the patient:

CRONOS Plan-. Monitoring protocol of the pharmacological treatment plans for the Alzheimer's disease

Administrated Test yes no

In which year we are? (0 - 1)	
In which season we are? (0 - 1)	
In which month we are? (0 - 1)	
Tell me today's date? (0 - 1)	
What week's day is it today? (0 - 1)	
In which nation we are? (0 - 1)	

In which Italian region we are? (0 - 1)	
In which town we are? (0 - 1)	
What is this city's name? (0 - 1)	
To how floor we are? (0 - 1)	
Repeat: "bread, house, cat". The first repetition doing the score. Repeat even when patient repeat correctly, max 6 times (0 - 3)	
Counting bashful from 100 deleting 7 for five times 93 - 86 - 79 - 72 - 65 (if he doesn't complete this test, then to make to spell back the word WORLD (0-5) D L R O W)	
Ask the repetition of last three subject (0 - 3)	
Shown a clock or a pencil asking what is its name (0 - 2)	
Repeat this sentence: "TIGER AGAINST TIGER" (0 - 1)	
Takes this sheet and fold up it and takes its on table (0 - 3)	
Reads and performs that is write on this sheet (close eyes) (0 - 1)	
Writes a sentence (with subject and predicate) (0 - 1)	
Copying this picture (woven pentacols) (0 - 1)	

Max total score = 30

Total score [_____]

Total sore corrected for age and learning [_____]

ADJUSTMENT COEFFICIENT OF MMSE FOR AGE AND EDUCATION CLASSES IN ITALIAN POPULATION

Age's interval	65-69	70-74	75-79	80-84	85-89
0-4 years	+0,4	+0,7	+1,0	+1,5	+2,2
5-7 years	-1,1	-0,7	-0,3	+0,4	+1,4
8-12 years	-2,0	-1,6	-1,0	-0,3	+0,8
13-17 years	-2,8	-2,3	-1,7	-0,9	+0,3

The second test administered to patient is the ALD¹⁷, or rather the Daily Life Autonomy:

CRONOS plan – Monitoring program of pharmacological treatment plans for the Alzheimer’s disease.

Score

A) DOING BATH (tub, shower, sponge)

- | | | |
|---|---|--------------------------|
| 1 | 1. Doing bath himself? (enters and goes out from tub alone) | |
| 1 | 2. Has help’s need to clean a specific body part (as back) | |
| 0 | 3. has help’s need to clean other body part. | <input type="checkbox"/> |

B) DRESSING (takes dresses from drawers, included underclothes, dresses, using belt or suspenders)

- | | | |
|---|---|--------------------------|
| 1 | 1. takes dresses and dressing oneself without assistance. | |
| 1 | 2. takes dresses and dressing and lacing shoes without assistance | |
| 0 | 3. you need have assistance to dress and lace shoes | <input type="checkbox"/> |

C) TOILETTE (going into bath for miction and evacuation,, cleanig, dressing)

- | | | |
|---|---|--------------------------|
| 1 | 1. goes to bath, he cleans and dressed again without need of assistance (can use means of support as baton, deambulator or small wheels chair, can use night vase or comfortable emptying them to the morning) | |
| 0 | 2.. It needs assistance in to go in bath or in to clean or in to dress again him or in the use of the night vase or the comfortable one | |
| 0 | 3. not going to bath for evacuation. | <input type="checkbox"/> |

¹⁷ <http://www.centroalzheimer.it/medcronosadl.htm>

D) MOVING

- 1 1. moving to bed or sofa without assistance (eventually with canadeses o deambulator).
- 0 2. doing this moving always with assistance.
- 0 3. stay always into bed.

E) DEFECATED AND URINES CONTINENCE

- 1 1. fully control of defecated and urines.
- 0 2. occasional "incidents".
- 0 3. it requires assistance to control defecated and urines , use catheter, is incontinent .

F) FEEDING

- 1 1. without assistance.
- 1 2. assistance also to cut the meat or to butter the bread.
- 0 3. is assisted to eat or partly fed or fully parenteral fed

TOTAL SCORE

The next test is an addition to ADL, the IADL¹⁸, that is the Daily Instrumental Life Autonomy:

¹⁸ <http://www.centroalzheimer.it/medcronosiadl.htm>

CRONOS plan- Monitoring protocol of pharmacological treatment plans for Alzheimer's disease.

Score

A) ABILITY TO USE TELEPHONE

- 1 1. uses telephone oneself.
- 1 2.doing also same known numbers.
- 1 3. answers to telephone but not composes numbers.
- 0 4.is incapable to use telephone.

B) DOING EXPENSE

- 1 1. doing expense autonomously.
- 0 2. is able to do also small purchases.
- 0 3.is able to do purchases always assisted
- 0 4.isn't able to do expense

C) COOKING

- 1 1. cooking meals and serves them autonomously
- 0 2. cooking meals also if someone proxy the ingredients.
- 0 3. it heats meals already ready , or prepares meals in wrong way and don't has a suitable feeding

0 4.it need of ready meals and assistace.

D) HOUSE'S CURE

1 1. succeeds to autonomously deal with the house or with occasional help for the heavy jobs

1 2. succeeds in effecting the light domestic jobs as to wash the dishes, to refer the bed, etc.

1 3. He/she succeeds in effecting the light domestic jobs but it is not able of to maintain a level suitable of cleaning.

0 4. It needs help for all the cleanings of the house.

0 5. It is completely disinterested to any domestic matter.

E) DOING LAUNDRY

1 1. Washes the whole own laundry.

1 2.washes only the small garments.

0 3.the whole laundry must have done from others.

F) MOVES OUTSIDE HOUSE

1 1.autonomously travels, serving of the public services or with is car.

1 2.makes use of taxi, but it's not able to use public service.

1 3. it travels on public service only assisted or accompanied

0 4.travels in car or in taxi when is assisted or accompanied by others.

0 5. cannot travel at all.

E) DRUG'S ADMINISTRATION

- 1 1. Is able to assume correctly drugs.
- 0 2. is able to assume drugs if in precedence already prepared alone the drugs.
- 0 3. isn't able to assume drugs alone.

F) USE OF OWN MONEY

- 1 1. provides in autonomous way to his own finances (account, make checks, pay lease and other expenses to go to bank), checks own entrances
- 1 2. handles the expenses and daily accounts, but it needs help for the greatest operations (to go to the bank, to make checks, to shop, etc)
- 0 3. isn't capable to handle proper money.

TOTAL SCORE

Last is administrated the Hachinski Ischemic Score¹⁹:

CRONOS plan- Monitoring protocol of pharmacological treatment plans for Alzheimer's disease.

Acute beginning	[2]
Stairs deterioration	[1]
Symptoms' fluctuation	[2]
Nighttime confusion	[1]
Relative personality's maintenance	[1]
Depression	[1]
Somatic troubles (neurological not focal signs and symptoms)	[1]

¹⁹ Hachinski V. C., Iliff L., Duboulay G.H., McAllister V., Marshall J., Ross Russell R.W., Syman L.- Cerebral blood flow in dementia- Arch Neurol

Emotional weakness (spastic smiling and weeping)	[1]
Hypertension	[1]
Cerebral ictus progress	[2]
Lateralized focal symptoms	[2]
Lateralized focal sigs	[2]
Atherosclerosis' signs in other districts (ex: IMA or AOAI)	[2]
Total	[_____]

4.6 Conclusions

The answer to the therapy with acetylcholinesterase's reversing inhibitors for the treatment of the Alzheimer's disease it appears of modest dimensions: in average only 2 patient every 10 essays show a positive answer to 3 months and solo 1 on 9 it maintains it to 9 months.

The Cronos Plan, had the objective followings:

- 1) to improve the knowledge of the population cuts' characteristics from the Alzheimer's disease and treated with anticholinesterasic medicines;
- 2) to appraise the appropriateness of the treatments;
- 3) to widen the definition of the bearly profiles of drugs ;
- 4) to identify possible varying for the optimization of the effectiveness profile of the medicines.

The cards of the patients are been analyzed enlisted in the period September 2000 - December 2001, comparing the information with the data of available follow-up up to February 2003. The study has been conducted on 118 Unities of Evaluation Alzheimer (UVA), among the 503 established to national level. A list of 7395 patients of it, of which 1933 have been excluded by the analysis results, in how much already in treatment with acetylcholinesterase's inhibitors. The final champion therefore results of 5462 patients. For the effectiveness evaluation, they have been considered "responders" the patients that, to 9 months of treatment, they had a difference of score to

the Mini Mental State Examination (MMSE), in comparison to the basal one, of 2 points. For the evaluation of bearly, the onset of the first adverse event has been considered signalled in the period of study of 9 months.

Results have been: the population treated within the Cronos project is constituted in great measure by patients of female sex, of age middle 79 years. The 17% of the patients introduced a concomitant pathology and him 8% it was in treatment with other active medicines on the SNC (more frequently antidepressants). Around the 64% of the patients you/he/she has been treated with donepezil, 32% have received rivastigmina and the 4% galantamina. A patient on 7 has interrupted the therapy within three months for the onset of adverse events, the attainment of a score of inferior MMSE to 10 (what it represented criterion of exclusion) and a clinical evaluation of ineffectiveness. In average only 2 patient every 10 essays have shown a positive answer to 3 months and solo 1 on 9 has maintained it to 9 months. Adverse events are recorded in 1 patient on 7 and of these the 36% has induced to interrupt the treatment. The more frequent adverse events are results the gastrointestinal and cardiovascular troubles.

In conclusion, the results of the Cronos project, as it regards the effectiveness of the colinesterasis inhibitors, they appear rather disappointing.

The Cronos project is finished March 30 2003, but the medicines have remained prescribed.

5. New therapy's perspectives for Alzheimer's disease

5.1 The genic therapy

The possibility to prevent the neurons' degeneration during progressive nervous system's disease, as in the Alzheimer's disease, it would represent a meaningful progress in the care of this serious disease. This discovery, all Italian, of Rita Levi Montalcini, it seems to give a concrete hope for the experimentation of a new save-memory drug.

The nervous system's growth factors, nerve growth factors (NGF), constitute a group of natural proteins that show a notable ability in to prevent the neuronal dead in animal models.

5.1.1 What the NGF is

The NGF function, and of other neuronal trofins, mainly consists in to promote the cells target's differentiation and in to guarantee once its survival that has reached the full structural and functional maturation. This action is generally denominated with the term "trofism".

In the last decade the studies on the NGF have shown that the concept of trofic action must entirely have seen again and inserted in a notion that is not improper to define revolutionary in the biological field. The trofic term, in fact, as is mentioned, each time was attributed one determined substance it showed him able to allow the survival of a cells' population. Numerous hormones, vitamins and other various nature's extracellular messengers, included the growth factors, they are endowed with this action. The trofic action, in substance, according to this conception, it consisted in the 'make to be well' the cells target allowing the survival of it.

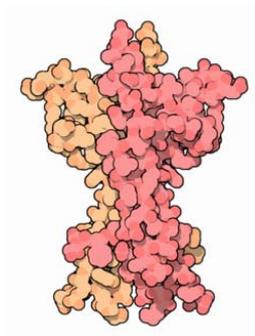


Fig. 15: *The nerve growth factor*

This factor is of fundamental importance for the nice nervous system's survival and the sensorial neurons. The NGF is released by the target cells and it is activated only when the bond happens with the active of receptor's site (TrkA), and it's interiorizing.

The principal obstacle in the use of such substances is constituted by the necessity to make to reach at brain substance concentrations of such entity not to be able to be assumed with the normal streets of administration.

5.1.2 Why the NGF

At the present moment the only medicines approved by the FDA for such pathology are the the Ach's inhibitors: they increases the acetylcolin levels and therefore they improve the cognitive performances. Such medicines are at the present moment of scarce effectiveness since the actual street of administration, oral, it doesn't allow the attainment of good results needing dosing of such entity to determine heavy collateral effects. This involves the choice of new therapeutic strategies. One of this dall is represented' use of the nervous growth factors (NTF). To the actual state have been individualized 100 of them.

The prototype of such substances is the NGF: it's produced from the hyppocamp cortical neurons and communicated through colinergic receptors up to the cellular body.

Such receptorial mechanism allows to modulate the neurons function is lasting the development that during the life, even if such mechanism has not been yet completely clarified.

In the Alzheimer the production of NGF doesn't result decreased, however its level of use reduces him. This makes to think that there are difficulty of transfer in the centers of use.

The observation that in the animal models the improvement of the NGF's transfer involves the deceleration of the cellular death has also induced the study of the effects of such transfer in the man.

The genic therapy could constitute the mean to move NGF to the zones well locate into encephalon. And' in progress currently a clinical trial in phase I.

5.1.3 The NGF as drug

The first tests on the man seem to give promising results. An American study published on 'Natures Medicinè' shows in fact that and' possible to increase the levels of the neuronal growth factor (NGF) in the brain, halving so the speed of the cognitive decline.

Investigations more deepened on a deceased patient have confirmed besides that the NGF increase stimulates the new neurons' generation. "The genetic therapy with NGF cannot take care of the Alzheimer, because it doesn't stop the formation of the amyloid plates on which the neuronal-degeneration depends - explains the author Mark H. Tuszynski, of the university of the California of You Jolla, San Diego. Nevertheless, the scientist adds, the deceleration of the cognitive decline from us gotten is 10 times superior to the benefits observed with the actual therapies ". For this "could be convenient to combine the genic therapy with the conventional cares, that inhibit the deposit of the amyloid fibers"²⁰.

5.1.4 An eyewash against Alzheimer's disease

"The molecule NGF (the nervous growth factor), administered as eyewash it reaches the cerebral neurons, it improves the cognitive abilities and it allows a new therapeutic approach against the Alzheimer. The discovery, published on the magazine Brain Research, is of a group of the CNR's researchers and the university in Rome 'Campus'."

New and interesting perspectives in the care of the Alzheimer's disease, thanks to an eyewash that contains the NGF molecule. A drop of this substance is able to reach the neurons of the basal pros-encephalon and to prevent its death. And' this the result of clinical studies conducted by Luigi Aloe of the neurobiology and molecular medicine (Inmm) institute of the national suggestion

²⁰ <http://www.molecularlaboratory.it/news/view.asp?n=2442>

searches in Rome and by Alessandro Lambiase of the oculistic university Clinic in Rome "Campus."

In the last years the nervous growth factor has received a lot of attention as therapeutic potential acting in the Alzheimer's disease and currently, the use of this molecule in the disease treatment asks for the intra-cerebral administration in cerebral areas proximity struck by the pathology.

In the future the molecule can be administered during the first disease phases as simple eyewash, to reduce e/o to stop the pathology evolution, that esteems him, today in the world, strikes around 15 million people of which around 4 American million. In the next 20-30 years the U.S. citizens affections from disease of Alzheimer will be over 10 million and the Europeans around 15 million.

The results gotten by the two Italian researchers make part of a long and intense collaboration and activity of base search, pre-clinic and clinic, that has brought in precedence to the discovery of the NGF therapeutic effectiveness on corneal and skins ulcers of various origin, published in the most important international scientific magazines, among which Lancet, being incapable to cross the blood-encephalic barrier.²¹

The clinical study opens new interesting perspectives in expensive of the Alzheimer's disease, the researchers have underlined as the based eyewash on the NGF molecule succeeds in acting on the neurons of the basal pro-encephal preventing the death of it. Then this eyewash could improve the patients' cognitive abilities struck by the Alzheimer's disease.

²¹ <http://www.cnr.it/cnr/news/CnrNews?IDn=1564>

5.2 The etanercept

"By the Alzheimer in ten minutes!"²² it recites this way an article of the 'Journal of Neuroinflammation' of a few months regarding the etanercept, in fact it seems that this drug is potentially curative for the Alzheimer's disease.

Through a study has been injected, with intra-spinal injection, etanercept to a 81 year-old man, struck by light form of Alzheimer, and according to what brought by the magazine the elderly person memory was clearly improved after ten minutes.

The etanercept is a medicine used for the rheumatoid arthritis and with any use in the Alzheimer's disease. It is a medicine of band H, therefore completely free but administrated alone through hospital firms. This medicine acts on the TNF-alpha, that is the tissue necrosis' factor alpha, busy in the inflammatory trials and if produced in great quantities it would damage the cerebral cells.

Obviously these are given encouraging but it are a study effected on an only person and the real effects of the care or the duration of the effects are not even known.

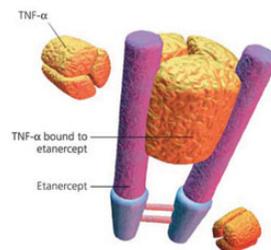


Fig. 16: *etanercept action on TNF-alpha*

²² <http://www.jneuroinflammation.com/content/5/1/3>

When it comes with the health it always needs to be cautious. For example in past there have been some studies that tied a regular aspirin's assumption to a smaller probability to contract the Alzheimer's disease.

Recently however a new article appeared on Lancet Neurology is of the opposite opinion, the aspirin doesn't reduce the probabilities to contract the Alzheimer. The administration of low aspirin doses has some least effects, if not void, on the patients' cognitive decline without considering that if it's assumed for long periods behaves a serious risk of hemorrhages, especially in the most elderly patients. In determined cases is decided to take care of an disease even if there could be some collateral effects, but in the cases in which the benefits are inferior to the possible complications it is well always to avoid determined drugs.

5.3 New drugs

The new therapeutic perspectives for care the Alzheimer's dementia have three important addresses:

- 1) to inhibit the neuronal toxic peptid Abeta 42, or to promote its clearance;
- 2) to inhibit the fibrils genesis;
- 3) to prevent the protein Abeta 42 neuronal toxic effects.

5.3.1 Protein Abeta 42's inhibition

The physiological metabolic way is that in which the alpha-segretasi enzyme intervenes that it starts the metabolism of APP (Amyloid Precursor Protein) toward the form not amyloid or rather without the production of amyloid fibrils. Under pathological conditions, it prevails the action of the beta-segretasi enzyme, that intervenes in the external portion of the APP and it produces the protein

Abeta part amino terminal; a second enzyme, gamma-segretasi, hidrolize APP inside the membrane, producing the carbossic terminal portion.

The gamma-segretasi it is a molecular complex constituted by 4 subunits: alpha 1, PEN 2, presenilina and nicastrina. It can act on the fragments of APP forming sub fragments of different greatness.

The pharmacological inhibition of the beta-segretasi it represents a promising therapeutic target as it regards the Alzheimer's disease. Of the 2 iso-forms of beta-segretasi (BACE 1 and BACE 2), the first one is that express in the Central Nervous System.

Some peptide-mimetic of BACE have been produced 1, that have a statine in their structure. Such inhibitors could represent some medicines endowed with an advantageous safety profile, as suggested by the evidence that the mice deprived knock-out of BACE they are vital and apparently normal.

Other possible intervention is that to load of the gamma-segretasi that, as we have seen, it detaches from APP the carbossic terminal part. But the intervention on this enzyme is very delicate, as it hidrolizes the Notch receptor, an important target for the processes of cellular differentiation that could be compromised, for example, to load of the admitting system.

The gamma-segretasic activity could be more than completely inhibited, perhaps modulated: this ownership is of some FANSs (ibuprofen, indometacin, sulindac), but not of the aspirin.

Them, with a mechanism that doesn't involve the ciclossigenasi, they induce the peptides' production with a amino acids' number inferior to 40 and therefore not pathological. An increasing attention is turned to is her of it that seems to reduce the amyloid deposits through the reduction of

the cholesterol levels that, probably, if increased, strengthen the BACE 1 street that it is amyloid producing.

5.3.2 Clearance inhibition of beta-amyloid peptide

It's what has been done with the vaccination procedures thanks to which is tried to remove the amyloid from the extracellular deposits.

Surprisingly the vaccine doesn't show only preventive action, but it shows curative in mice that have developed the disease.

The vaccine action's mechanism is referable to the direct or indirect activation of the microglia that would be, in last analysis, responsible of the amyloid plates' dissolution.

After the comforting results on the animal, the studies is passed in phase I and II. The trials, however, have been suspended, for the onset of 5 Central Nervous System's inflammation cases on 360 patient essays.

5.3.3 Fibrils genesis inhibition

The fibrils genesis inhibitors include some molecules that able is revealed to get ready among the amyloid fibrils. The fibrils dissolution has been realized through synthetic peptides that has the ability to tie the beta leaflets or through drugs that involve from intercalary fibrils, what the daunomicina, the tetraciclins and the carvedilolo.

Zinc is brought to be crucial for the Abeta peptide aggregation and the zinc chelation with clioquinolo (parasiticide) it seems to reduce the amyloid load.

A study pilots (phase II) has been conducted in 36 patients which the parasiticide has been administered for 36 weeks. Meaningful variations are not been observed as it regards the scoreses

related to the cognitivity, but after opportune sick stratification in base to the level of disease gravity, clinically a meaningful effect has been shown in the most serious patients. The stricken group has shown less severely a meaningful reduction of the Abeta's levels in the plasma.

5.3.4 Prevention of amyloid protein's neurotoxicity

Such possibility draws sprout from a series of recent data that correlate the neuronal degeneration induced by the Abeta protein to the anomalous activation of the cellular cycle through the proteins cyclines' type production (D1, A, E) and an enzyme (beta polimerasis DNA) that activates an anomalous replication of the DNA that brings to cellular death through the production of factors as the p53 (the apoptosi is had before the cell can pass from the phase S to the replication phase).

These anomalous enzymes could represent the point of attack of a "selective" pharmacological intervention, that don't introduce that is the risk to interfere with the physiological cellular cycle that develops in proliferating cells.

5.4 The vaccine

A vaccine against the Alzheimer's disease. It's not reality but the researcher's team of Roger Nitsch of the university of Zurich has started an experimentation in such sense.

The first results have been in Zurich from the dott. Nitsh team, and are defined by the experts "very promising".

Nitsch has experimented the new vaccine together to an international group.

The vaccine has note the objective to prevent the plates formation, that are the cause of the neuronal dead, immunizing the brain from the plates deposit. The result, to one year, it is considered

more positive: in the vaccinated patients (already struck by the disease), in fact, him and' recorded a notable deceleration in the degeneration of the cognitive. trials In 20 patients on 24 of the group of the Swiss (the whole international study includes 298 patients) researcher him and' besides recorded the development of antibodies against the beta-amyloid proteins changed, disease responsible and a meaningful deceleration of the pathology.

The development of cerebral edema in some subjects had forced in 2003 to interrupt the clinical trial to make a will a first vaccine against the Alzheimer. To the epoch was thought about exposing the subjects organism to small beta-amyloid protein's quantities, the protein that goes to form ample cerebral plates in the subjects struck by disease contributing to the neurodegeneration process so that to stimulate the immunitary system to quickly destroy it.

Today some researchers of the neuroscience's metropolitan institute of Tokyo have developed a new DNA vaccine that, in the tests on mice, has shown to be effective and deprived of collateral effects. Containing the code for the protein expression, the vaccine it stimulates some cells to produce a light excess of beta-amyloid, enough however to stimulate a reaction of the immunitary system. In the mice submitted to vaccine, as is reported in a researchers' article the appeared on the last number of the Proceedingses of the National Academy of Sciences (PNAS), the accumulation of beta-amyloid protein was inferior of 30% in comparison to the controls in head to four months and of the 50 percent in the one year-old turn.

5.4.1 AN-1792

The pharmaceutical firms Elan and Wyeth have introduced the results of an experimental treatment against the plates that bait the mechanism responsible of the Alzheimer's disease in the brain, also not improving the cognitive abilities jeopardized by the disease.

AN-1792 was the drug's name experimented for its potential to stimulate the immunitary system to "recognize" and to attach the beta amyloid plates. A mixture had been developed in base to the theory that the treatment with beta-amyloid could activate the immunitary system to produce antibodies that attach the plates.

In July 1999 the newspaper "Nature" it brought the first promising pre-clinic studies on the animals. These studies on the mice genetically programmed for producing beta amyloid plates in own brain has shown two facts: in the trans-genic mice still cures the vaccine has avoided the formation of the plates and injected in the mice that had already developed the plates in the brain has reduced the number of it.

On the base of these pre-clinic studies the FDA (Food and Drug Administration) in the United States and the agency for the control of the Medicines in England gave the permission to perform clinical studies of Phase I on the man to appraise the safety and the medicine bearly in people with light or moderate Alzheimer's disease. In England the participants were 80 and in the United States 24.

The results of these studies of Phase I, introduced in 2000, suggested that the vaccine pits well born from the man. Besides they showed, that a part of the participants developed amyloid antibodies.

On the base of these results was started in October of 2001 a study of Phase IIA in the United States and in Europe, that would have had to have the two year duration. The clinical studies of Phase IIAs are a smaller version of those of Phase II with the same objectives: that is to appraise the medicine effectiveness, to establish its best dosing and to confirm its safety. In this experimentation are been inserted around 375 people with light or moderate Alzheimer's disease; 300 have been random to receive the AN-1792 and the remainders to receive the placebo.

In January 2002 Elans Corporation and Wyeth-Ayerst Laboratories, the two pharmaceutical firms that experimented the medicine, announced the experimentation's suspension after four participants, that had received multiple doses of AN-1792, they introduced symptoms of central nervous system inflammation. When other 11 participants developed the same symptoms toward the end of February 2002, the scientists of the independent Committee for the Control and the Safety they concluded that the clinical study had to be jammed and that the medicine didn't owe to be administered anymore.

The researchers will keep on following all the study's participants to check their state of health and to take care of them in the case they appeared some similar symptoms. All the patients that have introduced central nervous system's inflammation symptoms have received the appropriate medical cares and, according to the two pharmaceutical firms, they are improved or they are reestablished.

The tests directed to feel the effectiveness of the therapy, called AN-1792, had been interrupted in the month of January of 2002 after four encephalitis' cases were verified, but the researchers had kept on following the patients conditions. Has emerged that the patients that had received the vaccine succeeded in getting best results in the tests that tried the memory, in comparison to those that had not assumed it, and assumed, besides, an examination to the brain of the four patients a meaningful reduction has been observed by the characterizing substance the amyloid plates that typically they fill the spaces among the brain cells in the Alzheimer's patient.

The exact cause of the brain inflammation is not note yet. The researchers are trying to understand the motive for which some of the participants have developed the symptoms and to establish what conclusions can be drawn by the picked data. These results are very unlucky but not entirely unexpected. The medicine's producers have recognized that to provoke the immunitary

system to attach an own protein could have some potential risks, among which the inflammation. These risks had been explained to the participants during the application of the informed consent, necessary for the share. Although these results have not confirmed the promises of the AN-1792, the study has shown the validity of a search clinic protocol carefully structured and checked. The inflammation's symptoms have been identified at the right moment and the researchers have quickly acted.

5.4.2 DNA vaccine

Seen the results gotten with the molecule AF-1792, with which was thought about exposing the organism

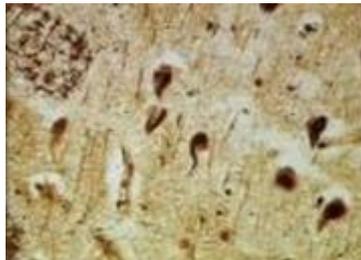


Fig. 17: *DNA vaccine*

to small doses of amyloid protein to stimulate the organism, or better the immunitary system, to destroy it. Today some researchers of the neuroscience's metropolitan institute of Tokyo have developed a new DNA vaccine that, in the tests on mice, has shown to be effective and deprived of collateral effects.

Containing the code for the protein expression, the vaccine it stimulates some cells to produce a light excess of beta-amyloid, enough however to stimulate a reaction of the immunitary system. In the mice submitted to vaccine, as is reported in an article of the researchers appeared on the last number of the Proceedingses of the National Academy of Sciences (PNAS), the accumulation of

protein beta-amyloid it was inferior of 30% in comparison to the controls in head to four months and of 50% in the one year-old turn.

5.4.3 New generation vaccine

The rise up of Alzheimer's disease has been brought back to the presence of the plates that are formed when fragments of the beta-amyloid protein detach him from the cellular membrane and conglomerate in the brain.

"These peptides are toxic for the brain: they contain in fact 40-42 amino acids that accumulate in the cerebral cells, preventing them to communicate the one with the others and provoking the death of it", has declared Cordis to the News-bulletin doctor Frank Mattner.

The new generation vaccine is directed to arrest the peptided accumulation with 42 amino acids inducing the immunitary system to attach the peptides. This is not the first attempt to develop a vaccine for the Alzheimer on the base of immunitary reactions, as already said in precedence. "Our approach is different. We won't use the protein self", has declared Cordis to the News-bulletin.

The project's partners will use the "mimotopo" instead, a sequence able to stimulate the antibodies production against the degenerate form of the protein, without attaching the natural form. "The 'mimotopo' is on purpose created for attaching the beta-amyloid container 42 amino acids and to induce the immunitary reactions desired ", has explained.

The approach has already been experimented. The researchers will also assemble him on the peptides, that contain less than 42 amino acids, since I am also individualized in the plates responsible of the cerebral cells' death.

To today has not been set some vaccination program against these peptides yet. In the next three years, the project's partners will conduct both the phases pre-clinic is the first clinical phases of the new vaccine's development.

To the project, that is coordinated by Affiris, partner of the industry and the academic environment of Austria, Germany and Spain stick. The last objective is to develop a therapeutic vaccine, but the project's partners have not excluded the vaccine use which measures preventive for the Alzheimer.

"We must first of all show that the vaccine works, before being able to think about using it to preventive purposes", the doctor Mattner has declared²³.

References

Hoojmans C. R., Kiliaan A. J.(*Eur J Pharmacol*, 29/2/2008)

Sorbi S. (*Neurol Sci*, 2003), Genetica della malattia di Alzheimer

Sorbi S., Massaro F. (*Neurol Sci*, 2004), Neurodegenerazioe nelle demenze e amiloidosi

Heijer D., Geerlinge M., Hoebeek F.(*Arch. Gen. Psychiatry*, 2006), Use of Hippocampal and Amygdalar Volumes on Magnetic Imaging to Predicted Dementia in Cognitively Intact Elderly People

Birks J.S., Melzer D. (1999), Donezepil for mild and moderate Alzheimer disease

²³ Cordis, 15.01.2007

European Public Assessment Report EPAR (CPM/243/98 rev. 1), Rivestigmine

Magni E., Binetti G., Bianchetti A., Rozzini R., Trabucchi, Mini-Mental state Examination: a normative study

Hachinski V. C., Iliff L., Duboulay G. H., McAllister V., Marshall J., Ross Russel R. W., Syman L., Cerebral blood flow in dementia, Arch Neurol

Paoletti, Nicosia, Clementi, Fumagalli- Neuropscofarmacologia

www.coreadihuntington.it

www.parkinson.it

www.neuropsychiatry.it/alzheimer.pdf

www.pubmed.gov

www.neurologia.it

www.pharmacologyonline.org

www.parkinsonitalia.it

www.reteparkinson.it/pubblicazioni/neurostimolazione

www.alzheimer.it

www.centroalzheimer.it

www.epicentro.iss.it/cong_leb/scafato.htm

www.infoalzheimer.it

www.neuroinf.it/medico/alzheimer/decorso/

www.molecularlab.it

www.afisna.com/soclav/20010323_BorrDan_ginkgo.htm

www.farmaexplorer.it

www.xagenait.com

www.farmacoteca.it

www.progettoalzheimer.org

www.bioportfolio.com

www.smart-publications.com/hearts_attacks/salvia.php

www.alzheimer_cronos.org

www.accademiaxl.it