Ageing and Neurologic Disease

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THE PROCESS OF AGEING IN THE DIFFERENT ORGANS AND APPARATUSES

Ageing is a complex and heterogeneous process defined as the gradual, time-dependent decline or loss of physiological functions; its rate and speed vary from species to species, from organ to organ within the same species, down to the tissues and cells of the same organism (Diamanti-Kandarakis et al., 2017; Carmonna JJ et al., 2016): the process of ageing is a kind of mosaic, for example kidney and lung get older faster.

During the process of ageing there is loss of some cells, and massive anatomical-functional alteration in different apparatuses (Harrison's, *Principles of Internal Medicine 19th ed*., McGraw-Hill Medical). Here are some examples of these modifications resulting from ageing.

Skeletal Muscle System

Decrease of muscle mass, muscle contraction and of the number of mitochondria;

Decrease of bone mass leading to osteopenia and osteoporosis leading to high risk of fractures;

Degeneration of intervertebral discs and high risk of hernias, joint pains, spondylosis;

Degeneration of cartilage that leads to postural instability and to gonarthrosis with reduction of the articular line.

Central and Peripheral Nervous System

Decrease of the mass of the CNS and the vascular flow;
Decrease of the number of neurons, of gray substance, and of neurotransmitters and consequently of neuron connections;
Decrease of visual acuity and night vision; modification of the crystalline lens with risk of cataracts;
Arthrosis and reduced mobility of anvil, hammer and stirrup in the ear.

Respiratory and Cardiovascular System

Decrease of elastic capacity and muscle response in the lung;
Reduction of oxygen saturation;
Decrease of muco-ciliary clearance;
Decreased diastolic filling;
Degenerative phenomena of the arterial vessels;
Increased pressure.

Gastrointestinal System

High risk of diverticulosis and fecaloma formation due to decreased intestinal motility.

Urinary System

Decrease of kidney mass (-40%) due to loss of nephrons;
Reduction of glomerular vasculature and alteration of renin secretion;
Reduction of renal flow, glomerular filtration and tubular function;
Muscle weakening and reduced capacity in the bladder;
Increase of volume in the prostate with pollakiuria and dysuria.

Immune System

Immunosenescence that is characterized by changes in the immune system and in the apoptosis process, induced by oxidative stress (Ventura et al., 2017; Fulop et al., 2018);
Increase of inflammatory response;

Decrease of efficacy of B antibody and T response, Dendritic cells, macrophages and neutrophils;
Reduction of antibody response and Increased autoantibody response.

Endocrine System

Reduction of testosterone and of the GH / IGF-1 axis with some symptoms such as sarcopenia (reduction of strength and muscular endurance, loss of mass, tone and muscle strength);
Osteoporosis;
Reduction of appetite and food intake;
Drop in libido;
Cognitive and psychogeriatric symptoms;
Anaemia;
Increased cardiovascular risk;
Alteration in hypothalamic–pituitary unit (Diamanti-Kandarakis et al., 2017).

Molecular Alteration

Ageing is accompanied by multiple **molecular alterations** (Diamanti-Kandarakis et al., 2017). There is increase of several molecular alterations involving DNA, RNA or proteins, such as an increase in genomic instability, chromosome structural abnormalities, epigenetic alterations, DNA cross-linking and frequency of single-strand breaks, a decline in DNA methylation, loss of DNA telomeric sequences, an alteration of posttranslational changes of proteins structure (deamidation, oxidation, cross-linking, and nonenzymatic glycation) and of mitochondrial structure (Harman et al., 2001). It has recently been discovered that pathophysiological mechanisms of ageing may be also accompanied by alteration of micro RNAs functions and stem cell exhaustion (Lopez-Otin et al., 2013).

THE FRAIL ELDERLY PATIENT

The capability of an organism to keep balance and to adjust to change may promote longevity, frailty and disease (Diamanti-Kandarakis et al., 2017). There are three manners of ageing:

Common/normal: which includes that part of the population that grows old with some disability and comorbility;
Successful ageing: which includes those people who have a physical, cognitive and functional performance above average;
Pathological ageing: which includes all frail patients.

Frailty is undoubtedly a negative predictor, predisposing to unfavorable clinical outcomes such as mortality, poor quality of life and disability. Being frail predicts likelihood of early death, higher disabilities, a much more frequent rehospitalization rate and more early institutionalization risks (Kelaiditi et al., 2013).

The intrinsic factors that are often associated with the development of a state of frailty are:

1) Sarcopenia: Sarcopenia is a geriatric disease caused by different factors such as: oxidative stress (ROS), changes in the endocrine system, loss of the regenerative capacity of cells. Its onset may be favored by some diseases such as heart failure, respiratory failure, immobilization syndrome.

2) Malnutrition: When malnutrition is established, the descending parable of the state of frailty is accelerated. The following may contribute to the development of malnutrition: early satiety, slow digestion, alteration of taste and smell, alvo disorders, psychic causes (depression, dementia), poverty and solitude. Weight loss in elderly subjects impacts on different organs and apparatuses (in particular on muscle, bone, immune system) and increases the risk of infections, immobility, hospitalization, mortality, anaemia, cognitive impairment.

3) Dementia: A person with dementia, 8 times out of 10, is also a frail elderly patient (cp. pharagraph **a**).

4) Life habits: Some aggravating factors of a state of frailty seem to be education level, economic problems, lack of social and family support, and smoking. On the other hand, a well balanced diet such as the Mediterranean diet, regular moderate exercise and a longer period of study and of

intellectual activities seem to be good guarantee against early cognitive and physicological decay.

Modifiable lifestyle factors and a multidomain intervention – including physical activity, cognitive engagement, active social life and a healthy diet (such as the Mediterranean diet) – are a key strategy for protection against risk of developing frailty and may delay the progression and secondary appearance of adverse results related to cognitive frailty, improve or preserve the cognitive functions and may help to prevent cognitive decline (Kelaiditi et al., 2013; Ngandu et al., 2015, Phillips C et al., 2017).

NEUROLOGIC DISEASES AND AGEING

The most common neurologic diseases in older people are dementia, Alzheimer's disease, Parkinson's disease and depression (Harrison's 2017; Pinessi, et al., 2015).

a) Dementia

Dementia is a serious geriatric syndrome, an intrinsic factor of frailty and a powerful predictor of mortality and instability. This general term is used to describe a deficit in two or more functional cognitive areas diagnosed for at least 6 months.

Dementia is dramatically increasing in the general population and its evolution is progressive. Dementia is characterized by impairment of acquired cognitive capacity. It affects the memory, the intellectual and linguistic skills, and is usually accompanied by radical changes in personality and sometimes in motor skills: in particular dementia is a progressive loss of memory, concentration, thinking process, orientation, comprehension, calculation, learning ability, language, and judgment and executive functions (Rossor et al., 2007). Given prolonged life expectancy, dementia cases are increasing dramatically in the general population, in particular in persons over 85 years of age (Savva et al., 2009; Ritchie et al., 2002; Milne et al., 2008).

There are primitive forms of dementia: Alzheimer's disease (the most frequent degenerative dementia), Trisomy 21, Frontotemporal dementia (FTD), Lewy body dementia (LBD), Progressive supranuclear paralysis, Corticobasal degeneration, Parkinson's disease, Huntington disease (HD), Prion disease. Secondary forms of dementia can be reversible or associated

with an organic clinical condition: vascular disease; endocrine disease (diabetes, hypo- or hyperthyroidism, hypoparathyroidism, hypocortisolism, hypercortisolism) Infectious-inflammatory CNS (Infectious pathology: HIV, cysticercosis, lue, borelliosis, Whipple disease, chronic meningitis, brain abscess); Toxic-deficiency (Nutritional causes: B12 deficiency, folate, thiamin, dehydration; Exogenous drugs or toxic substances); Lupus, rheumatoid arthritis, Antibodies antiphospholipid syndrome); Intracranial expansive processes (Brain tumors; Chronic subdural hematoma); Chronic renal and liver failure; Drugs; Different causes and different origins such as: severe anaemia, polycythemia vera, porphyria, paraneoplastic syndromes) (Pinessi et al., 2013).

Diagnosis of dementia is based on clinical examination, on neuropsychological tests, on neuroimaging and on laboratory tests (blood and liquor) (Pinessi et al., 2013). Psychiatrists, neurologists and geriatricians are involved in the management of dementia and in the assessment of the patient.

A general objective examination must always be accompanied by a neurological examination; Anamnesis should check for signs suggestive of dementia or of other diseases. It is important to investigate:

Clinical history: familiarity, trauma, signs of alcoholism, drug abuse, nutritional status (folic acid and vitamin B12 cause reversible dementia);

Other diseases or some possible confounding factors that could mimick dementia such as encephalopathies, dysthyroidism, hyper or hypothyroidism, respiratory failure, liver failure, renal failure, diabetes, arterial hypertension, obstructive sleep apnea syndrome (OSAS);

Pharmacotherapy; a possible further cause of reversible dementia is iatrogenic;

Psychiatric/neurological pathology.

Cardiovascular diseases and the risk factors of vascular cerebropathy;

Neurological examination: Focal neurological signs such as paresis, sensory alterations, aphasia (a focal deficit suggests an ictal cause); Movement and walking (parkinsonism, ataxia of the march, myoclonus).

The most frequently used test for neuropsychological diagnosis is the MMSE (Mini Mental State Examination) (Petersen et al., 2011), which is a global evaluation scale useful for monitoring dementia. It is a 30-point test to evaluate cognitive function, orientation over time and space, memory (recording and memory), attention and computational skills, language and visuospatial function. Based on the score (normal> 24-27 / 30) dementia is defined:- Mild 20-24;- Moderate 10-19;- Severe <10.

The stages of the diagnosis of dementia include: evaluation of cognitive impairment; etiology of dementia; severity of cognitive impairment; behavioral changes; social, family and environmental situation.

There is no effective treatment of degenerative dementias. Cholinesterase inhibitors and memantine may be useful in mild or moderate disease phases (Pinessi et al., 2013).

It is important to intervene at an early stage of cognitive decline to slow or prevent progression to dementia also with some approaches not strictly pharmacological (Kelaiditi et al., 2013; Ngandu et al., 2015, Phillips C et al., 2017), (cp. last paragraph).

b) Alzheimer's Disease

Alzheimer's disease is one of the most common neurologic diseases, a deterioration of memory and other cognitive domains that leads to death within 3 to 9 years after diagnosis. It is the most common form of dementia, and 50-70% of all dementias is Alzheimer's disease (Querfurth et al., 2010). It is a fact that, with the gradual increase in the population of the elderly, Alzheimer's disease has become a major sociodemographic problem in industrialized countries and developing countries. It has a prevalence of 1% in individuals 60-64 years old, but it exponentially increases with age, reaching 24-33% in subjects over 85 years of age. This number is expected to double every 20 years, in relation to the ageing of the world's population and now Alzheimer's disease is considered a priority in terms of public health.

Alzheimer's disease is a complex and heterogeneous progressive disorder of the central nervous system and is the most common neurodegenerative disease.

The disease was first described in 1906 at a conference in Tübingen, Germany by Alois Alzheimer, as a "peculiar severe disease process of the cerebral cortex." Alois Alzheimer reported the histopathologic findings of neuritic plaques and neurofibrillary tangles in the brain of a 53 year old

woman with personality change and progressive dementia. More than one hundred years have passed since its first documentation, many aspects of the pathophysiology of AD have been discovered and understood, however gaps of knowledge continue to exist.

It is characterized by extensive and selective neuronal loss; Increased astrocytes; diffuse plaques in neocortex, neuritic plaques and synaptic alterations; numerous amyloid plaques; abundant neurofibrillary tangles (NFTs) in selectively vulnerable regions of the brain: deposition of amyloid plaques and neurofibrillary tangles represent the typical markers of the pathology. The preponderant pathogenic hypotheses are dysregulation of β-amyloid production and metabolism. An imbalance between production and clearance, and aggregation of peptides, may cause accumulation of β-amyloid and this excess may be the initiating factor in Alzheimer's disease. Accumulation of misfolded proteins in the ageing brain results in oxidative and inflammatory damage, which in turn leads to energy failure and synaptic dysfunction (Querfurth et al., 2010; Singh et al., 1997; Sanabria-Castro et al., 2017; Querfurth H NEJ 2010 Kang J, 1987; Goldgaber D 1987; Goedert 1966; Johson 1996; Yankner 1996; Yankner BA. 1996; Arriagada 1992; Kosik KS. 1993).

An important challenge in the field of neurodegenerative diseases is the early and timely diagnosis of the disease. For most neurodegenerative diseases, the underlying causative agent for the disease remains unknown and the diagnosis of neurodegenerative diseases related to ageing (dementias, etc.) is made on the basis of the presence of distinctive clinical features (McKhann et al., 2011). The first clinical description of Alzheimer's disease was that of 1984 by McKhann, updated in 2011, which claimed that to suspect AD it was necessary to diagnose deficit of memory associated with deficiency of at least another cognitive domain that lasted for at least six months, after excluding the causes of secondary dementia (McKhann et al., 2011). After more than thirty years, diagnosis still remains essentially clinical even if other criteria were introduced by Doubois (Doubois et al., 2007) and by the McKhann team (McKhann et al., 2011) (National Institute on Ageing and Alzheimer's Association) with some morphological and functional markers (PET and markers for β-amyloid) (Blennow et al., 2015).

In the last 15 years there has been massive research towards identifying preclinical markers of diseases such as Alzheimer. The most recent attempt

includes the notion of mild cognitive impairment (MCI), initially identified by the Mayo Clinic on the basis of a cohort study of adults suffering from AD (Petersen et al., 1999). The Mayo Clinic study found that before the emergence of the clinical symptoms of AD, subclinical memory decline was observed in those subsequently developing AD (Petersen et al., 1999).

It is an age-related degenerative disease, as the principal risk factor for Alzheimer's disease is age (Querfurth et al. 2010). Other risk factors include, beside advanced age, head injury, low level of education, depression, diabetes, smoking, environmental toxicity, manual work, cardiovascular disease. The best way to prevent Alzheimer's disease is the correction of cardiovascular risk factors: it is a fact that diabetes, hypertension and heart disease increase the production of β-amyloid.

The onset modality is typically subtle, with an initial short-term memory deficit and topographical orientation in known pathways, language disorder, behavioral and cognitive disorders, gnosic, praxic and emotional defect.

Natural history of the disease begins with the onset (initial accumulation of asymptomatic β-amyloid) that may occcur 20 years before the clinical onset, which corresponds to time 0. At the clinical onset follow mild, moderate and advanced phases of the disease. The average duration of the disease is 8-10 years, with an inter-individual variability.

It affects the memory, thinking, orientation, comprehension, learning, language, and judgment. In particular: Alzheimer's disease produces progressive memory loss, difficulty in solving problems, disorientation in time and space, changes in behavior and personality, and impairments of insight, judgment, executive functions, praxis and other cognitive functions (Singh and Guthikonda, 1997).

Treatment of patients with Alzheimer is difficult, because there is currently no specific effective therapy. The drugs currently used are cholinesterase inhibitors and memantine, an NMDA receptor antagonist (Pinessi et al., 2015).

In spite of a lot of ongoing clinical trials and a lot of experimental new drugs, no cure or drug has been able to delay or halt the course of Alzheimer's disease. New findings seem to show that cognitive impairment can be prevented or delayed even in the absence of new

drugs by promoting changes in behavior and by managing vascular risk factors (Ngandu et al., 2015) (cp. last paragraph).

In fact, different forms of non-pharmacological treatment for Alzheimer's disease are being studied, consisting of behavioral interventions, psychosocial support, cognitive training and physical activity. These measures may be resorted to in order to complement the pharmacological treatment and have shown positive results in the overall clinical management of the patient (Pinessi et al., 2015). Moreover recent studies indicate that cognitive interventions and maintenance of adequate levels of physical activity may even have the potential to delay the onset of Alzheimer's Dementia (F. Gomez-Pinilla et al., 2008, Curlik er al., 2013, Chang et al., 2010) (cp. last paragraph).

c) Parkinson's Disease

Two hundred years ago, James Parkinson first described the disorder that bears his name (Lang et al., 1998): in 1817 James Parkinson, an English doctor, described in his essay on "shaking palsy" the characteristic movement disorders observed in some patients (Lees et al., 2007).

Parkinson's disease is a neurodegenerative disorder due to interaction between genetic and environmental factors characterized by the coexistence of motor and non-motor symptoms and constitutes the second neurodegenerative disease after Alzheimer's disease.

It is characterized by the progressive death of selected but heterogeneous populations of neurons including dopaminergic neurons of the *pars compacta* of the *substantia nigra*. Loss of dopamine projections from the *substantia nigra* to the *putamen* causes the fundamental motor disorders of Parkinson's disease. The mechanisms responsible for cell death in Parkinson's disease are largely unknown. Increasing evidence suggests that in the neuronal death in the *pars compacta* of the *substantia nigra* may be involved apoptosis, mitochondrial dysfunction, oxidative stress, increased free radical production, the actions of excitotoxins, deficient neurotrophic support, and immune mechanisms. Symptoms occur when 70% of neurons of *substantia nigra pars compacta* have been damaged (Oertel et al., 1996).

The classic triad of major signs of Parkinson's disease is made up of tremor, rigidity, and akinesia (Gibb 1988; Hughes 1993). The condition typically develops unilaterally in the upper limbs but progresses to become bilateral and later involves postural instability and gait disorder. Later

complications include response fluctuations, declining levodopa response and dyskinesia (Oertel et al., 1996).

In addition to the primitive motor deficits, PD includes dysfuntion of higher order motor control. Non-motor symptoms of PD include cognitive deficits, behavioral disorders, autonomic disturbances and sleep.

The average age of the insurgence of Parkinson's disease (PD) is approximately 60 years, but likelihood of insurgence increases with age. In actual facts, age is one of the most consistent risk factors, and with the progessively increasing age of the general population, a significant increase in Parkinson's disease will occur in the future (Lang et al., 1998).

The diagnosis of Parkinson's disease is made on the basis of clinical criteria and is based on the presence at the neurological objective examination of resting tremor, rigidity, bradykinesia and postural instability (Pinessi et al., 2013). Misdiagnosis is also an important problem, because the syndrome of parkinsonism may have a number of different causes, such as drugs, Wilson's disease, and other neurodegenerative diseases.

The therapy is exclusively symptomatic and currently there is no treatment available that can change the evolution of the disease. Drug therapy is aimed at correcting the deficit of dopaminergic transmission and there are several classes of antiparkinsonian drugs including levodopa, decarboxylase inhibitors, dopaminergic agonists, monoamine oxidase inhibitors, anticholinergics, dopaminergic agonists and NMDA receptor inhibitors. Surgical approaches and non-pharmacological approaches, such as targeted physical activity interventions, are also being attempted to complete drug therapy (Pinessi et al., 2015).

d) Depression

Depression is a condition which almost all people experience in relatively mild forms many times in their lives. Depression meriting clinical attention is long-lasting, and severe enough to interfere with normal life. In addition to a depressed mood, the patient is typically lacking in both mental and physical energy to an extreme degree, he or she has the irrational feeling of worthlessness and/or guilt and may frequently think of death and suicide.

Major depressive disorder (MDD) is a global disease burden that affects over 300 million people worldwide (Ferrari et al., 2010). It is a heterogeneous disorder with a highly variable course, different sub-

divisions, different treatments; its pathogenesis has not yet been fully understood. Late-life depression occurs in persons 60 years of age or older among whom it may be very common. It is often associated with coexisting medical illness, cognitive dysfunction, or both (Belmaker et al., 2008; Taylor NE).

Older people may be prone to a higher proportion of depressing events, but causes of depression in later life are different. Causes may be attributed to a variety of diseases; life factors and psychological states of mind may contribute to the worsening of depression: stressful and negative events, bereavement, illness (especially chronic pain, stroke or fracture), medical treatment side effects, dementia, memory loss, finantial problems, long lasting social and relantionship problems (especially lack of social support) (Penninx et al 1996); Penninx et al., (1996) report that depressive symptoms increase with the number of illnesses patients are likely to suffer from. Some diseases seem to be more conducive to depression than others: conditions which create chronic pain, such as arthritis, were found to be more likely associated with depression than were serious but less painful conditions such as diabetes. Psychological state may also be an important factor in some cases, with various real or imagined shortcomings in capabilities, such as dementia and memory loss correlated with depressive symptoms. Lifestyle factors, such as financial problems or long-term social and relantionship problems may also be exacerbating factors.

The diagnostic criteria for major depression include observation of a marked change of mood, characterized by sadness or irritability, or anhedonia, accompanied by at least several psychophysiological changes, such as disturbances in sleep, changes in appetite, or sexual desire, energy level, crying, suicidal thoughts, and slowing down of speech and action. These changes must be observed over a minimum of 2 weeks and must interfere considerably with work and family relations (Lebowitz et al., 1997, Miller et al., 2000).

Screening elderly people for depression is very important because depressed older adults are at increased risk of suicide and because depression may be a manifestation of cognitive decline or a risk factor for dementia (Belmaker et al., 2008). It is also worth considering that older depressed people run the risk of developing dementia or pseudodementia.

Beside pharmacotherapy or psychotherapy as first-line therapy, some non strictly pharmacological approaches, social and physical activities may

be important to prevent the beginning or worsening of the depression process in elderly people. Depressed older adults should be encouraged to increase their social active life, engagement in pleasurable activities and social interactions, and physical activity (Belmaker et al., 2008, cp. last paragraph).

AGEING AND THE PREVENTION OF A STATE OF FRAILTY IN A MULTIDOMAIN INTERVENTION*

In the face of a multitude of drug and clinical trials failures, we now know that some neurological diseases cannot yet be cured: prevention and projects aiming to change life style may be an important way to manage some of these diseases related to ageing. In addition to improving research in the field of pathophysiology of diseases, diagnostics and research of new drugs, prevention and multidomain intervention should be extended because they may be the best way to manage some diseases related to age. Interventions aiming to change some lifestyle factors seem to be necessary to successfully fight some diseases. Older adults should be encouraged to increase their social active life, to increase engagement in pleasurable activities and social interactions, to intensify physical activity and improve nutrition. Those lifestyle factors changes may help some people even after cognitive decline and a state of frailty has already begun.

Recent studies have demonstrated that modified lifestyle factors are a key strategy for maintaining brain health during ageing and enhance brain and cognitive reserve. A multidomain intervention, including physical activity, cognitive engagement, active social life and a healthy diet (such as the Mediterranean diet), are strategic for protecting against frailty and may delay the progression and secondary appearance of adverse results related to cognition, they may improve or maintain the cognitive functions and may help to prevent cognitive decline (Kelaiditi et al., 2013; Ngandu et al., 2015, Phillips C et al., 2017).

A randomized controlled clinical trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) had the goal to assess the effect on cognitive health of improved diet, physical exercise and mental training while providing regular health advice and cardiovascular health monitoring (Ngandu et al., 2015).

Between 2009 and 2011 the FINGER clinical trial enrolled 1,260 men and women (mean age 60 years) who were randomly assigned to a control group, and to a treatment group. All of them with some risk for dementia. Members of the treatment group were then directed to follow a regimen of diet, exercise and cognitive training and received periodic clinical examination. Control group participants, on the other hand, received only basic health advice.

In comparison with the control group, the intervention group (631 participants) received a mix of nutritional guidance (healthy balance of protein, fat, carbohydrates, dietary fibers and salt and restrictions on consumption of sugar and alcohol), cognitive training (different cognitive tasks to enhance executive function (planning and organizing), memory improvement and mental speed) and physical exercise (physical training, aerobic exercise) and postural balance exercises; the subjects' cardiovascular condition was also more intensely monitored (regular checkups of metabolic and vascular health, regular measurement of weight, blood pressure, and hip and waist circumference).

The study provided good evidence that a combination of improved diet, physical exercise, mental and social stimulation, and management of cardiovascular problems can improve cognition even after age 60, maintaining cognitive functioning and preventing cognitive impairment. The multidomain lifestyle model used in the FINGER trial2 is going to be tested in different populations and in different settings across the world (US pointer, Mind-China, Singer, UK-finger study).

As the elderly population is constantly growing, projects of multidomain interventions aiming to change some modifiable risk factors such as diabetes, hypertension, obesity, physical inactivity, smoking, depression might be important in the management of diseases related to ageing and have an important role not only in the prevention of chronic diseases but are also socioeconomically relevant (Livingston et al., 2017, Toumilehto et al., 2001).

BIBLIOGRAPHY

Arriagada PV/Growdon JH et al. (1992): "Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease." In: *Neurology* 42, pp. 631-639.

Belmaker RH/Agam G (2008): "Major depressive disorder." In: *N Engl J Med*, Jan 3, 358/1, pp. 55-68. Review.

Blennow K/Zetterberg H (2015): "The past and the future of Alzheimer's disease CSF biomarkers-a journey toward validated biochemical tests covering the whole spectrum of molecular events." In: *Front Neurosci*, Sep 29, 9, p. 345.

Carmona JJ/Michan S (2016): "Biology of healthy aging and longevity." In: *Revista de Investigación Clínica* 68, pp. 7-16.

Chang M/Jonsson PV/Snaedal J et al. (2010): "The effect of midlife physical activity on cognitive function among older adults: AGES – Reykjavik Study." In: *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 65/12, pp. 1369-1374.

Curlik DM/Shors TJ (2013): "Training your brain: do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus?". In: *Neuropharmacology* 64, pp. 506-514.

Diamanti-Kandarakis E/Dattilo M/Macut D/Duntas L/Gonos ES/Goulis DG/Gantenbein CK/Kapetanou M/Koukkou E/Lambrinoudaki I/Michalaki M/Eftekhari-Nader S/Pasquali R/Peppa M/Tzanela M/Vassilatou E/Vryonidou A; COMBO ENDO TEAM (2017): "Mechanisms in endocrinology. Aging and anti-aging: a Combo-Endocrinology overview." In: *Eur J Endocrinol*, Jun 176, 6, pp. 283-308.

Dubois B/Feldman HH/Jacova C/Dekosky ST/Barberger-Gateau P/Cummings J/Delacourte A/Galasko D/Gauthier S/Jicha G/ Meguro K/ O'brien J/Pasquier F/Robert P/Rossor M/Salloway S/Stern Y/Visser PJ/Scheltens P (2007): "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria." In: *Lancet Neurol*, Aug 6, 8, pp. 734-46. Review.

Ferrari AJ/Charlson FJ/Norman RE et al. (2013): "The epidemiological modelling of major depressive disorder: application for the Global Burden of Disease Study 2010." In: *PLoS One* 8/7, pp. 1-11.

Fulop T/Larbi A/Dupuis G/Le Page A/Frost EH/Cohen AA/Witkowski JM/Franceschi C ([1960], 2018): "Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?". In: *Front Immunol*, Jan 10, 8, pp. 1-13.

Gibb ERG/Lees A (1988): "The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease." *J Neurol Neurosurg Psychiatry* 51, pp. 745-752.

Goedert M/Trojanowski JQ/Lee VMY (1998): "The neurofibrillary pathology of Alzheimer's disease." In: SB Prusiner, *The molecular and genetic basis of neurological disease*, Boston: Butterworth-Heinemann.

Goldgaber D/Lerman MI/McBridge OW et al (1987): "Characterization and chromosomal loclization of a cDNA encoding brain amyloid of Alzheimer's disease." In: *Science* 235, pp. 877-880.

Gomez-Pinilla, F (2008): "Brain foods: the effects of nutrients on brain function," Nature Reviews. In: *Neuroscience* 9/7, pp. 568-578.

Harman, D (2001): "Aging Overview." In: *Annals of the New York Academy of Science*, Apr 9, 28, pp. 1-21. Review.

Harrison's (2017): *Principles of Internal Medicine 19th*. Columbus OH: McGraw-Hill Medical.

Hogan MJ/Staff RT/Bunting BP/Deary IJ/Whalley LJ (2012): "Openness to experience and activity engagement facilitate the maintenance of verbal ability in older adults." In: *Psychology and Aging* 27/4, pp. 849-854.

Hughes AJ/Daniel SE/Blankson S/ Lees AJ (1993): "A clinicopathologic study of 100 cases of Parkinson disease." In: *Arch. Neurol* 50, pp. 140-148.

Johson GVW/Jerkins SM (1996): "Tau protein in normal and Alzheimer's disease brain." In: *Alzheimer Dis Res*, pp. 138-154.

Kang J/Lemaire HG/Unterbeck A et al. (1987): "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor." In: *Nature* 32, pp. 733-736.

Kelaiditi E/Cesari M/Canevelli M/ van Kan GA/Ousset PJ/Gillette-Guyonnet S/Ritz P/Duveau F/Soto ME/Provencher V/Nourhashemi F/Salvà A/Robert P/Andrieu S/Rolland Y/Touchon J/Fitten JL/Vellas B; IANA/IAGG. "Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group." In: *J Nutr Health Ageing,* Sep 17, 9, pp. 726-734.

Kosik, KS (1993): "The molecular and cellular biology of tau." In: *Brain Pathol* 3, pp. 39-43.

Lang AE/Lozano AM. (1998): "Parkinson's disease." In: *N Engl J Med*, Oct 15, 339/16, pp. 1130-1153. Review.

Lebowitz BD/Pearson JL/Schneider LS/Reynolds CF 3rd/Alexopulos GS/Bruce ML/Conwell Y/Katz IR/Meyers BS/Morrison MF/Mossey J/ Niederehe G/Parmelee P (1997): "Diagnosis and treatment of depression in late life. Consensus startement update." In: *JAMA*, Oct 8, 278/14, pp. 1186-1190.

Lees, AJ (2007): "Unresolved issues relating to the shaking palsy on the celebration of James Parkinson's 250th birthday." In: *Mov Disord*, Sep 22, Suppl. 17, pp. 327-34.

Livingston A/Sommerlad V/Ortega A (2015): "2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial." In: *Lancet* 385, pp. 2255-2263.

Lopez-Otin C/Blasco MA/Partridge L/Serrano M/Kroemer G (2013): "The hallmarks of aging." In: *Cell* 153, pp. 1194-1217.

Mattila RJ, "Epidemiology" in WC Koller (1987): *Handbook of Parkinson's Disease*. New York: Arcel Deeekr, pp. 35-50.

McKhann GM/Knopman DS/Chertkow H/Hyman BT/Jack CR Jr/Kawas CH/Klunk WE/Koroshetz WJ/Manly JJ/Mayeux R/Mohs RC/Morris JC/Rossor MN/Scheltens P/Carrillo MC/Thies B/Weintraub S/Phelps CH (2011): "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." In: *Alzheimers Dement*, May 7, 3, pp. 263-269.

Miller KE/Zylstra RG/Standrige JB (2000): "The geriatic patient: a systematic approach to maintaining health." In: *Am Family Physician*, Feb 15, 61/4, pp. 1089-1104.

Milne A/Culverwell A/Guss R/Tuppen J/Whelton R (2008): "Screening for dementia in primary care: A review of the use, efficacy and quality of measures." In: *Int Psychogeriatr* 20, pp. 911-926.

Ngandu T/Lehtisalo J/Solomon A/Levälahti E/Ahtiluoto S/Antikainen R/Bäckman L/Hänninen T/Jula A/Laatikainen T/Lindström J/Mangialasche F/Paajanen T/Pajala S/Peltonen M/Rauramaa

R/Stigsdotter-Neely A/Strandberg T/Tuomilehto J/Soininen H/Kivipelto M (2015): "A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial." In: *Lancet*, Jun 6, 385/9984, pp. 2255-2263.

Oertel WH/Quinn NP, "Parkinsonism", in Brandt T/ Caplan LR/Dishgans J et al. (1996): *Neurological disorders: course and treatment*, San Diego: Academc, pp. 715-722.

Penninx BW/Beekman AT/Ormel J/Kriegsman DM/Boeke AJ/van Eijk JT/Deeg DJ (1996): "Psychological status among elderly people with chronic diseases: does type of disease play a part?". In: *J Psychosom Res*, May 40, 5, pp. 521-534.

Petersen RC/Smith GE/Waring SC/Ivnik RJ/Tangalos EG/Kokmen E (1999): "Mild cognitive impairment: clinical characterization and outcome." In: *Arch Neurol*, Mar 56/3, pp. 303-8. Erratum in: *Arch Neurol* 1999 Jun 56/6: p. 760.

Petersen, RC (2011): "Mild cognitive impairment." In: *N Engl J Med* 364, pp. 2227-2234.

Phillips, C (2017): "Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health during Aging." In: *Neural Plast*, Jun 12, pp. 1-23.

Pinessi, Lorenzo/ Gentile, Salvatore/Rainero, Innocenzo (2015): *Neurology Book*, Milano: Edi Ermes Edition.

Querfurth HW/LaFerla FM (2010): *N Engl J Med*, Jan 28, 362/4, pp. 329-344.

Rabassa M/Cherubini A/Zamora-Ros R et al. (2015): "Low levels of a urinary biomarker of dietary polyphenol are associated with substantial cognitive decline over a 3-year period in older adults: the Invecchiare in Chianti Study." In: *Journal of the American Geriatrics Society* 63/5, pp. 938-946.

Ritchie K/Lovestone S (2002): "The dementias." In: *Lancet* 360, pp. 1759-1766.

Rossor Martin/Growdon John (2007): *The Dementias*, Boston: Butterworth- Heinemann.

Sanabria-Castro A/Alvarado-Echeverría I/Monge-Bonilla C (2017): "Molecular Pathogenesis of Alzheimer's Disease: An Update." In: *Ann Neurosci*, May 24/1, pp. 46-54.

Savva GM/Wharton SB/Ince PG/Forster G/Matthews FE/Brayne C (2009): "Medical Research Council Cognitive Function and Ageing Study." In: *N Engl J Med*, May 28, 360/22, pp. 2302-2309.

Singh VK/Guthikonda P (1997): "Circulating cytokines in Alzheimer's disease." In: *J Psychiatr Res*, Nov-Dec 31/6: pp. 657-60.

Taylor, WD (2014): "Clinical practice. Depression in the elderly." In: *N Engl J Med*, Sep 25, 371/13: pp. 1228-1236. Review.

Tuomilehto J/Lindström J/JG Eriksson (2001): "Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance." In: *N Engl J Med* 344, pp. 1343-1350.

Ventura MT/Casciaro M/Gangemi S/Buquicchio R (2017): "Immunosenescence in aging: between immune cells depletion and cytokines up-regulation." In: *Clin Mol Allergy*, Dec 14, pp. 15-21.

Wilson RS/Mendes CF/De Leon/ Barnes LL et al. (2002): "Participation in cognitively stimulating activities and risk of incident Alzheimer disease." In: *JAMA* 287/6, pp. 742-748. Review.

Yankner, BA (1996): "Mechanisms of neuronal degeneration in Alzheimer's disease." In: *Neuron* 16, pp. 921-932.

Yankner, BA (1962): "New clues to Alzheimer's disease: unraveling the roles of amyloid and tau." In: *Nature Medicine* 2, pp. 850-852.