TRANSDISCIPLINARITY OF TIME RESEARCH IN BIO-MEDICINE

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The knowledge society is based on the research of time in transcausality and transdisciplinarity: the progress of civilization, sustainable development, information society etc. Physical, astronomical, calendrical, geological time – as it is structured in temporality (unidimensionality, irreversibility) – "flows" in the history, present and future of the Earth. Biological time signifies the life and its evolution in the vegetable and animal kingdoms. It is structured into phylogeny, ontogeny, transdisciplinarity (recapitulation), biorhythms and chronobiology. Human time is organized into an essential transdisciplinary triad: biological, psychological, sociological in chrono-medicine, -pathology, and -therapeutics. The research of time in bio-medicine represents a three-phasic process: ascendant (development), plateau (balance), descendant (involution). The tetrad of research on time in bio-medicine (phases 2 and 3) comprises 4 sciences: gerontology, geriatrics, anti-aging medicine and longevity sciences. The origin of the 4 sciences is preponderantly Romanian: Ilia I. Mecinikov (1845–1916) – 1908 Nobel laureate, terminology – gerontology and probiotic therapy; Constantin I. Parhon (1874–1969) – Vitamin E therapy (tocopherols, tocotrienols); Ana Aslan (1897–1988) – in 1952 in Romania, the first Geriatrics-Gerontology Institute in the world, therapy with Gerovital H_3® and Aslavital®; the team comprised of Simion (1902–1976) and Ion Oeriu – Folcisteines class U®, A®, P®; Corneliu E. Giurgea (1923–1995) – Piracetam (DCI)/Nootropil® and the Racetams class; the group comprised of C. Oniscu, Şt. Cilianu and D. Dobrescu – Meclosulfonate (DCI)/Romener®; the team comprised of Dan and Sorin Riga – the Antagonic-Stress® class. Gerontology, geriatrics, anti-aging medicine and the longevity sciences are progressing and creating in transdisciplinarity as part of the health-longevity medicine. Lipopigments (lipofuscin and ceroid pigments) are markers of biological time, oxidative stress and aging. They are also indicators (through process, reduction and therapeutic elimination) of the aging deceleration and of the biological time reversibility.

Key words: transdisciplinarity and transcausality; physical, biological and human time; gerontology – geriatrics – anti-aging medicine – longevity sciences; Romanian origins of these 4 sciences: I. I. Mecinikov, C. I. Parhon, A. Aslan, Oeriu team, C. E. Giurgea, Oniscu-Cilianu-Dobrescu group, Riga team; health-longevity medicine; lipopigments – biological time markers.

Live as if you were to die tomorrow.
Learn as if you were to live forever.

Mohandas Karamchand GANDI (1869–1948), outstanding Indian politician, "Father of the nation", also called MAHATMA (great soul) by the valuable Indian poet Rabindrahnath TAGORE (1861–1941)

THE KNOWLEDGE SOCIETY AND TIME RESEARCH

TRANSDISCIPLINARITY AND TIME

The progress of science, technology and informatics demands a new perspective – dimension – paradigm in *time* research and bio-medicine. Therefore, it is imperative to change the current approach and concepts, for new models and new strategies in the *time* sciences from biology, medicine, therapeutics, psychology, sociology and the knowledge society[6].

The "sustainable" development itself requires *time* as a coordinate (= durability) and the dynamic stability of space (of the system itself) in the building of human civilization. Thus, "durable" development integrates in perfect balance the ecosystem, protects resources, extends pollution-free regenerable energy, and finally preserves the planet's viability (conservation = *time* stability) – the Gaia transdisciplinary concept[19].

"Durable" development equals harmonious development. Both of them imply an anti-entropic structural dynamism *in time,* which can be transdisciplinary[13] built through trans-causality (Fig. 1).

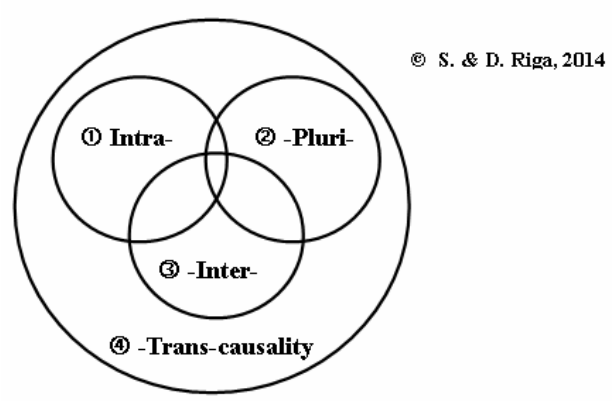

Fig. 1. Construction of intra→ pluri→ inter→ and trans-causality in phenomenology (logic) of transdisciplinarity.

PHYSICAL, ASTRONOMIC AND CALENDRICAL TIME

Time is defined and characterized in trans-disciplinarity as the following:

- one of the fundamental forms of moving matter existence, expressing the succession, simultaneity and the process interaction of objective reality;
- an ontological category that abstracts the universal property of all forms of existence to have a certain duration, positioning itself simultaneously or successively one in front of the other;
- a fundamental concept of physics, that distinguishes as a succession of events, the order in which they have started, are in progress and end.

Time is structured as a moment, interval or duration in the evolution and characterization of the actions, events, phenomena and processes – **temporal coordinate.** The essential characteristics of **temporality** (defined by comparative lining with the Euclidean tridimensional space) are the following:

- *uni-dimensionality* – the moments and stages are linearly succeeding, from the *past* (un-modifiable) throughout *present* (always relative) towards *future* (with a certain determined probability);
- *irreversibility* – past moments, ended on temporal coordinate are irreversible, irrecoverable, and non-repeatable.

Physical time (*astronomic*, basically identical to *calendrical time*) represents the dimension in which life processes develop, as they are established by physical and chemical *time-dependent* processes.

Physical time, by calendar it measures the geological history of the Earth – ***geologic time.*** It is divided into geologic era – characterized by its own flora and fauna (a paleontological criterion). Earth represents the "home" of life, humankind and civilization (Gaia concept)[19].

TIME IN BIOLOGY AND MEDICINE

Biological time represents a temporal dynamic conglomerate, in interrelationship with physical and chemical times, as a result of the uneven physical and chemical speeds at which biological processes take place, in the same body and also compared to one another[29].

Biological time represents the ***life*** itself, *vegetable* and *animal* kingdom[15], having the cell at the base, as the morpho-functional unit (the M. J. Schleiden's and T. Schwann's Cellular Theory).

In the animal biology of vertebrates, mammals, primates and humans, time is structured as a *biological progress*:

- in ***phylogenesis***/*biological diversity* – the history of life on Earth from the beginnings until the humans creation;
- in ***ontogenesis***/*life cycles* – the history of organism evolution from egg/zygote until adult-hood/death;
- and in *temporal* ***transdisciplinarity***/*the law of recapitulation* (the F. Muller's – E. Haeckel's Biogenetic Law: *ontogenesis* repeats/recapitulates some principal forms of *phylogenesis).*

Biorhythms (biological rhythms) are periodical variations of the biologic processes and phenomena; by origin they are endogenous and exogenous, by duration they are daily and nightly (circadian), monthly (estrous, menstrual, ovarian cycle), seasonal, annually etc.

Chronobiology studies the variations of specific life phenomena as a *function of time,* often manifested under the form of rhythmical oscillations. ***Chronopathology*** investigates disease characteristics (appearance, evolution) as a function of patient biorhythms. ***Chronotherapy*** comprises the treatment administration at the specific hours at which its action is most efficient.

Psychological time results from *over-integration of* physical → chemical → biological and nervous/cerebral times (according to Ludwig van Bertalanffy's General System Theory), in human psychical/personality structure-function (cognitive-logical and emotional-temperamental) and in their evolution-development (maturation, regression, involution). *Psychological time* evolves by quality and performance on the vector of normality – *mental health* or on the psycho-pathological one – *psychic disturbances*[37].

Sociological time is represented through human behavior at the individual level, and by human society at populational level. In the normality/ abnormality and moral/ethic registry, the individual develops normal or pathological behaviors on which *the society* becomes *healthy or unhealthy* (E. Fromm)[10].

Humans are structured and function into a **trivalent transdisciplinarity: *biological*** (somatic, physical) – ***psychological*** (psychical, mental, personality) – ***sociological*** (behavior, in action, fact maker).

In consequence, the human being is a *bio-psycho-social* trinomial[37] (Fig. 2), who evolves/ involves in a temporal trivalence: simultaneity and the interactions of 3 different types of time and biorhythms: *neurobiologic (substance), psychical (energy),* and *social (information).*

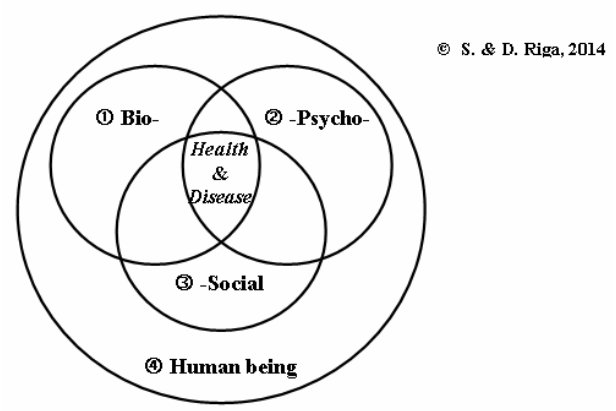

Fig. 2. The human being and construction of health (+)/(–) disease in the trivalent bio-psycho-social system.

Time functionality of bio-psycho-social system follows 2 antagonistic, opposite pathways:

- positive direction **(+)**, **anti-entropy**, ectropic, of organization and progress:
  sanogenesis (cause, dynamics, process) ➔ ***health, longevity*** (effect, consequence, finality, status); or
- negative way **(–)**, **entropy**, disorganization and regress:
  pathogenesis, morbigenesis (cause, process) ➔ ***diseases, pluri-pathologies, mortality*** (consequence).

CODING, SYMBOLISM AND TIME PHILOSOPHY

Time in biomedicine, science and culture as *aging* and *human longevity* represents a permanence (thus a *time* coordinate) of human civilization (that develops and progresses also on the coordinate *time*, in successive ages). The legends of time color the entire humanity.

Ancient India immortalizes mythological times through the undying Sanskrit ages of Indian literature: *Mahabharata* and *Ramayana*. They tell "into a symbolic code" about civilizations with ultra-technologies and gods with ages of thousands of years, that came down from the sky.

Greek and **Roman antiquity** have delighted humanity with a "mythological" demonstration of symbolism and integration of the 4 sciences of bio-psycho-social time: gerontology, geriatrics, anti-aging and longevity. *Time – Cronus* is personified in the pre-Socratic philosophy in the titan *Cronus-Kronos*, and in Romans by *Saturn*. Cronus and his wife Rhea (the 2nd generation of gods) have ruled the *Golden Age* of humanity (of the good human), which subsequently their son *Zeus* (3rd generation) degenerated into the *Iron Age* (the evil man). *Time,* as life span, everlasting and eternal is personified in Greek mythology by the goddess of eternal youth and logenvity, *Hebe*, and in Roman antiquity by *Juventas.*

In **ancient China,** *time* is respected and divined as a milestone and significance, as duration, longevity and immortality. The philosophical, cosmological, religious and ethical tradition of time is immortalized by *Taoism/Daoism* – in Latin: Tse/LaoZi. Causal, energetic, herbal and preventive medicine is centered around gaining harmony and balance. Together with science – the art of preparing remedies for longevity are the pillars of anti-aging medicine.

The Bible must be understood as a "historical code of time" of the human emergence, evolution and development in a bio-psycho-social trans-disciplinary plan. The Bible emphasizes a "time code" of Methuselah ages personified by Methuselah. Son of Enoch and grandfather of Noah, Methuselah lived 969 years (Adam only 930 years), becoming a symbol of longevity (Old

Testament). The Flood can be analyzed as "a temporal barrier" because life expectancy has plummeted – Abraham lived only 175 years.

Romanian literature "fix" the *time* and chronobiology – as hope/life span and eternity (so all the *time*) in the dimension of eternal youth, longevity and immortality[38]: the thrilling tale of *Youth Without Old Age and Life Without Death* (Petre Ispirescu – 1862, 1882). Such a fairy tale does not exist elsewhere in the world, in the folklore of other people.

TIME RESEARCH TETRAD IN BIO-MEDICINE

TIME, BIOLOGY AND MEDICINE

The tetrad (static enumeration) is organized in a **model → a dynamic system of time research in biology and medicine**. The temporal interval extends from the completion of growth and development (25 years), until the end of life. In this way, the system comprises a succession of comparable periods in a metabolic and energetic plain as well as morphological and functional.

By time and performance, the life stages are represented in a dynamic succession on 2 axes (vertical – performance, horizontal – time). By phenomenologically triphase modulation, the 3 periods of animal or human life are:

- youth – on an ascending vector →
- adulthood (with 3 stages: young, mature, old) – a plateau with a slowly descending slope, especially in the last stage →
- the old period (the third age/65–85 years old, the fourth age/85 years and beyond, longevity) – on a descending vector.

The time research system in bio-medicine (© Riga, Riga, 2007) is represented in trans-disciplinarity through 4 secant circular surfaces in a systemic and dynamic interaction (Fig. 3). The system results from a continuous development of 4 sciences – presented in the temporal order of their emergence and substantiation: **gerontology, geriatrics, anti-aging medicine and the longevity sciences**[32].

"The parentage" of the 4 bio-medical sciences of time is predominantly Romanian. It starts with Nobel laureate **Ilia I. Mecinikov** (1845–1916) – parental ancestry through Moldavian boyard Nicolae Milescu Spătarul (1636–1708), **Gheorghe Marinescu** (1863–1938) – world first treaty *La Cellule nerveuse* (**1909**), forefront studies in neurogerontology – neuro-geriatrics and **Constantin I. Parhon** (1874–1969) – world first endocrinology treaty *Les secrétions interne* (**1909**), first papers on clinic gerontology and geriatrics.

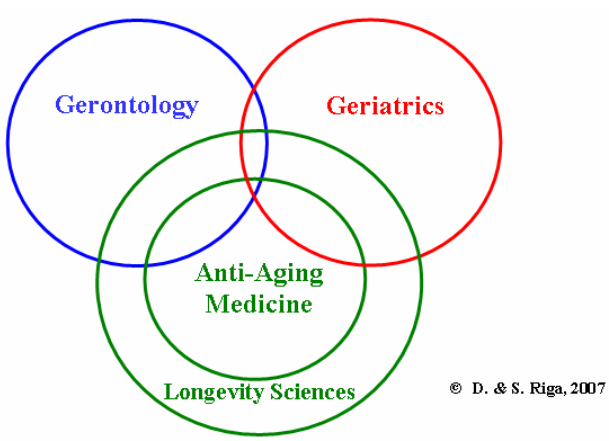

Fig. 3. Pattern-system of time research in bio-medicine.

Romania establishes a new world priority**,** through **institutionalization of geriatrics**[36]: in **1952** the team formed by C. I. Parhon – **Ana Aslan** (1897–1988) creates **the world first Geriatrics Institute**, which from **1974** becomes **the National Institute of Gerontology and Geriatrics**. In the following period, **1958–1988**, the institute is headed by acad. prof. dr. Ana Aslan, world author of the first geriatric medicine and anti-aging drugs – *Gerovital* H_3 and *Aslavital.*

Romania continues to **score the first new advances in the field**, by innovative therapies in anti-aging medicine and longevity sciences: **Simion Oeriu** (1902–1976) – the *Folcisteines* class, **Corneliu Giurgea** (1913–1995) – the *Racetams* class etc.

GERONTOLOGY AND GERIATRICS

Gerontology represents a branch of *biology* and *medicine* (hybrid concept), which studies the process of *aging* (cause, dynamics) and *senescence* (effect, status). ***Biologic gerontology (bio-gerontology/experimental gerontology)*** searches aging in the vegetable and animal kingdoms, from monocellular to multicellular, to chordates, vertebrates, mammals and primates.

Medical (clinical) gerontology[3,25] investigates normal aging on humans – *senescence* and pathological aging – *senility,* on a biological and psychological plan (human trivalency: bio-psycho-social). ***Social gerontology and geronto-***

demography examine human being on social and sociological plan, as an individual, population and society, viewing the health and public assistance/private assistance through: legislation, health policies, institutional and administrative aspects as well as economic and financial ones on a national and global scale[32].

The Nobel laureate for Medicine (**1908**), **Ilia I. Mecinikov** (**1845–1916**) is the world founder of **gerontology**. In the year **1903**, he **relates the term *gerontology*** (**Gr. *geron, -ontos* = old person, *logos* = science**) thus become universal in science, biology and medicine.

In the **1901–1914** period, in *Annales de l'Institut Pasteur*, he publishes *Études biologiques sur la vieillesse* and *Études sur la flore intestinale*, each in several parts, 2 monographs: *Études sur la nature humaine. Essai de philosophie optimiste*, Masson, Paris, **1903** (republished numerous times after) and *La prolongation de la vie. Essais optimistes*, A. Maloine, Paris, **1907** (1-ère éd), **1914** (2-ème éd). The books are an integrative synthesis in gerontology, are widely acclaimed contemporary, they have been translated into English and were sources of progress in bio-medicine. Last monograph is actually the first ***anti-aging medicine*** treatise in the world, divided into 9 parts, 34 chapters, 446 pages. The book provides a comprehensive analysis of the plant, animal and human senescence: *Études sur la vieillesse; La longevité dans la série animale; Études sur la mort naturelle – dans le monde végétal, le monde animal, dans l'éspèce humaine; Faut-il tenter de prolonger la vie humaine; Les rudiments psychique de l'homme; Sur quelques points de l'histoire des sociétés animales; Pessimisme et optimisme; Goethe et Faust; Science et morale.*

Geriatrics is *the medicine of elderly* – old, very old and rarely healthy longevous (3rd and 4th ages). Because of the persons last cycle of life, geriatrics must include poly-pathology / co-morbidities, especially with chronic manifestations. It becomes therefore a synthetic/full medicine, simultaneously encompassing family medicine, general and that of several specialties[32].

By progress, the **biology-medicine** binomial of gerontology[8,9] transdisciplinary develops a new complementary hybrid binomial: ***gerontology-geriatrics***[2,23]. Due to pioneer's works and world recognition, we will present only Romanian excellence.

ANA ASLAN STRATEGY IN GERONTOLOGY, GERIATRICS AND LONGEVITY

For 36 years **(1952–1988),** Acad. Prof. Dr. Ana Aslan imposed ***Romanian gerontology and geriatrics*** worldwide. Related to the communication sciences, impact, prestige and the international promotion of Romania, ***Ana Aslan geronto-geriatrics brand*** has become the most representative Romanian medicine worldwide.

We present a synthesis **of the 4 Ana Aslan concepts – Romania**[32].

1. ***The three-dimensional unitary concept of geronto-geriatrics (experimental-medical-social)*** was founded in practice and institutionalized by the creation and organization in the midle past century in Romania, of the scientific geronto-geriatrics: establishment on 22 January **1952,** the first *Institute of Geriatrics* worldwide. From the beginning, the Romanian geronto-geriatrics, the multidisciplinary institute, the fundamental, clinical and translational researches have been applied nationally. The concept institutionalization has then transformed into a national strategy in this field. Thus, the Institute has become a standard, and the Romanian pattern has rapidly been taken over on an international scale by numerous countries worldwide.

Due to the success and efficiency of elderly care and public health, in **1964** the *World Health Organization* President proposed it as a reference institution – an international model devoting its absolute authority and Romania priority in this field.

2. ***The global concept of elderly health centers at a national scale,*** signifying the extension and practical application in territory of the modern strategies in geronto-geriatrics. The concept materialization meant in the development of a *national medical network on aging prophylaxis and old age care, also on associated pathology.* To increase the quality of life, the Romanian example was subsequently applied in various countries by many health care networks and support systems.

In the same time, Romania has organized a *complementary network* of medical tourism with health benefits (approx. 30 locations) to synergistic harness the geronto-curative and prophylactic recovery wealth of natural landforms, mineral waters and balneo-physiotherapy.

3. ***The holistic concept of active geronto-prophylaxis,*** developed in *anti-aging medicine,*

given the fact that old age begins from juvenile years. There is no question about the necessity of this paradigm, but on efficiently applying and institutionalizing it. The concept is centered on eu-bio-trophic, regenerative, pro-vitality and pro-longevity medication, which interferes and efficiently decelerates the aging processes and effects. The exponent and practical result of this strategy is the Romanian drugs – *Gerovital H_3® and Aslavital®* – that aims to the therapeutic, biologic-metabolic and psycho-nervous activation of the human body, and the prevention and treatment of aging. It is essential to mention that the emergence of these two Romanian drugs has determined an explosion of competitive geronto-geriatric products worldwide.

Complementary, the Ana Aslan strategy of medico-psycho-social prevention/public health has been achieved by creating, in 31 October **1986,** at Roman city, town in Romania the *Third Age University,* with 4 faculties: *socio-political sciences, humanities, geronto-geriatrics* and *occupational therapy-hobbies.*

4. ***The integrative concept of healthy aging, active and useful,*** materialized by the *Ana Aslan Decalogue,* which represent the 10 strategic directions of achieving *well-being (wellness)* and of *life quality* at the third and forth age, according to the human genetic program.

The last 2 (two) Aslan concepts were presented by the author for the first time at the International Gerontology Conference in Merano, Italy, in **1956**, as 10 sanogenetic imperatives:

(1) *Food – the secret to life extension;*
(2) *Physical (activity) and movement;*
(3) *Training for old age;*
(4) *Critical age (age 40–65 years);*
(5) *The art and strength to have positive emotions;*
(6) *Chronic Disease Prevention and learning how to cope with them;*
(7) *Pre-geriatric and geriatric examination;*
(8) *Longevity – family and sanogenesis;*
(9) *Leisure in old age;*
(10) *Eu-bio-trophic and anti-aging treatment with Gerovital H_3®.*

ANTI-AGING MEDICINE AND LONGEVITY SCIENCES

Promotion of *health, active living, healthy longevity and quality of life* is the aim of ***anti-aging medicine*** *and* ***longevity sciences***.

Anti-aging medicine is a clinical specialty that extends the concept of preventive health care to embrace the very early detection, prevention and reversal of aging related diseases, coupled with the aggressive yet gentle disease treatment. Anti-aging medicine has accelerated the pace of advancements in health promotion and prevention, and is the most important new model for health care for this new millennium – Dr. Robert Klatz – President of *the American Academy of Anti-Aging Medicine*[17] (**2003**).

The essence of anti-aging medicine and longevity sciences is sanogenesis and the longevity construction, prevention and prophylaxis (primary, secondary, tertiary), anti-aging protection, geronto-prophylaxis[20] and aging deceleration.

Visionary founders of the *four bio-medical sciences* were performed the *transdisciplinary* creation. Our paper highlights the predominantly Romanian pathway[32].

1. Ilia I. Mecinikov (**Romanian** paternal descendant, born in **Russia**, and in the second half of life, the scientific activity in **France** at the Pasteur Institute in Paris, and Noble Prize for Medicine) has created into the **1900–1916** period the *probiotic medicine-therapy*: replacing through nutrition the pathogenic, infectious, toxic (bacteria and fungus) flora of the human intestine, with non-pathogenic, saprophyte, symbiotic and pro-biotic flora.

It is a pro-longevity nutritional therapy *(yoghurt, acidophilous milk, sour milk, kefir)*: eliminates constipation (pathogen residua), detoxifies the body (gut, liver, blood and other systems), stimulates tissue and blood flowing immunity (80% of the human immunity being localized in the intestines), ensures resistance, health, an active live and a healthy longevity.

After the **1960s**, modern medicine re-certificates the importance of pro-biotic therapy for health and longevity – selection:

– G. Lesnoff-Caravaglia, A. K. Hadjihristev, *Life-Styles for Long Life. Longevity in Bulgaria*, C. C. Thomas, Springfield, IL, **1988**;

– N. Trenev, *Probiotics. Nature's Internal Healers*, Avery, New York, NY, **1998**;

– W. L. Cowden, F. Akbarpour, R. Dicarlo, B. Goldberg, *Longevity. An Alternative Medicine Definitive Guide,* Alternative Medicine, Tiburon, CA, **2001**.

After the **1990s**, a real *pro-biotic* ⊕ *pre-biotic* ⊕ *anti-aging factors* industry is being developed

(only one example: *Potent Probiotic Acidophilus* with 100 mg *Citrus Pectin* contains 30 types of pro-biotic bacteria, in a quantity of 3 billion of live microorganisms / per 1 capsule).

2. Constantin I. Parhon (Romania), in the **1950s**, lays the foundation of the anti-aging therapy with *natural vitamin E (α, β, γ, δ tocopherols and tocotrienols):* Sub-chapter 26 C – *Researches of treatment with Vitamin E,* pp. 397–409, In: C. I. Parhon, *The Biology of Ages. Experimental and Clinical Researches,* Romanian Academy Publ., Bucharest, **1955** (26 chapters, 451 pages, 189 references).

Vitamin E has multiple specific and synergistic anti-aging actions (Parhon): liposoluble vitamin, strong natural anti-oxidant, vascular protection, anti-atherosclerotic factor, polyvalent bio-trofic activity – nervous, endocrine, muscular, osteoarticular, lymphatic ganglions (with specificity on the organs derived from the mesoderm).

The science progress in the **1980s** re-discoveries the anti-aging efficiency of Vitamin E: anti free radicals therapy, scavenger, anti-oxidative stress, anti-oxidant[26]. After 60 years, *The American Academy of Anti-Aging Medicine (A4M)* re-confirms the longevity therapy with Vitamin E – R. Klatz (A4M President), R. Goldman (A4M Chairman), *121 Ways to Live 121 Years… and More ! Prescription for Longevity,* A4M, Chicago, IL, **2005**.

3. Ana Aslan (Romania) between **1950–1988** has created the worlds first anti-aging, regeneration, eu-trophic therapy: drug class *Gerovital H_3®* (**1956**) and subsequently *Aslavital®*, applied after the original prophylactic, curative and recovery method.

The main active substance is novocain (procaine), stabilized by innovative pharmaceutical technology. Diversification of administration included: Gerovital H_3® – tablets, vials, creams, lotions, shampoos and Aslavital® – children lozenges, tablets and ampoules for adults.

Novocain is an ester, which hydrolyzes into two biologically active substances:

- an amino alcohol – *di ethyl amino ethanol (DEAE)*: scavenger, metabolic neutralizer of reactive oxygen species, nitrogen and sulfur, an indirect precursor of the cholinergic system (acetylcholine), that provides immediate and short-term memory and represents the para-sympathetic autonomic nervous system neuro-transmitter; and
- an acid, vitamin – *p-amino benzoic acid,* (PABA, vitamin H', H_2, B_{10}), folic acid component (vitamin Bc or M, other vitamin from B group).

Ana Aslan anti-aging revolution, Romania was rapidly taken over, copied and capitalized under other denominations and patronages, by different countries from the entire world.

The Gerovital H_3® – Prof. Dr. Ana Aslan phenomenon, brand, method and drug became (through reproductions and modifications, copying or additions): *K.H.$_3$®* (Germany), *Gero Vita G.H.$_3$* (Canada), *GH_3, GH_3 Gold , GH_3 Advance, GeroH_3, Gerovital H_7, Gerovital – Natura – Viga, Vitacel 7* etc.

4. The Simion and Ion Oeriu team (Romania), between the years 1950–1970, underpinned the crucial role of thiol -SH/-SS- disulphide in the functioning of anti-aging systems and mechanisms in biology (plant, animal), medicine, pathology and therapy. Research "brand Oeriu" characterized aging (normal and pathological) as a general, progressive dysmetabolism – amplified by age/time, and provoked through 3 specific anti-homeostatic processes:

– decrease of methyl groups (-CH_3);
– lowering of reduced, thiol groups (-SH);
– simultaneously with the increase of oxidized, disulfide groups (-SS-).

Correcting the 3 dysmetabolisms of biological time is through *Oeriu anti-aging therapy: Folcisteines class U® (human), A® (animal) and P® (plant),* patented as inventions in Romania and internationally. *Folcisteina U®* is an ortho-molecular donor of metabolically active -SH groups (anti-oxidative protection / marked metabolically by cyclization in thiazolidin carboxylic acid), enhanced by folic acid and stabilized by lithium and calcium sulfosalicylate:

– S. Oeriu, I. Tănase, *Biochemical aspects of aging*, pp. 273–288. In: N. W. Shock (ed.), *Biological Aspects of Aging,* Columbia Univ. Press, New York, NY, **1962**;

– S. Oeriu, *Proteins in development and senescence*, pp. 23–85. In: B. L. Strehler (ed.), *Advances in Gerontological Research,* vol. 1, Academic Press, New York, NY, **1964**;

– S. Oeriu, I. Oeriu, *Thiol Groups and Their Role in Biology*, Romanian Academy Publ., Bucharest, **1977** (332 pages, table of contents and summary in English).

S. Oeriu therapy (Romania) represents the anti-aging, anti-geriatric, anti-pathogenic and pro-longevity *therapeutic link.*

World scientific evidences and the challenge of time demonstrate the achievement of a real breakthrough in anti-aging medicine. In addition, *the Folcisteines class therapy* is the perfect complementary to the etio-pathogenic sequence of aging: *Free radical theory of aging and disease* and *Diseases of free radicals* – D. Harman (USA) and *Diseases of oxidative stress* – R. Cutler (USA), *CRC Handbook of free radicals and antioxidants in biomedicine*, vol. 1 and vol. 2, CRC Press – J. Miquel (USA)[22].

5. Corneliu E. Giurgea (1923–1962 in **Romania**, 1962–1995 in **Belgium**) created and developed during **over 40 years** (**1950–1995 years**) concepts, strategies and new drugs in neuro-sciences and anti-aging medicine.

Giurgea therapies – inventions, neurometabolic drugs – are defined by their actions – nootropics, anti-aging, anti-hypoxic agents, cerebro-metabolism activators, memory and cognitive enhancers:

- *piracetam* (DCI) – *2-oxo-1-pyrrolidine acetamide* (Eur. Pat. **1964**) and
- *etiracetam* (DCI) – *(R)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide* (US. Pat. **1987**).

Nootropic concept and *strategy* are pointed out in papers and textbooks – selection:

– C. Giurgea, *Fundamentals to a Pharmacology of the Mind,* C. C. Thomas, Springfield, IL, **1981** (10 chapters, 446 pages and 866 references);

– C. Giurgea, *The next decade in drug treatment of cognitive disorders*, pp. 137–146, In: G. Racagni, J. Mendlewick (Eds.), *Treatment of Age-Related Cognitive Dysfunction: Pharmacological and Clinical Evaluation*, S. Karger, Basel, CH, **1992**.

Anti-aging principles and strategies developed by Giurgea – selection:

– *Experimental behavioral pharmacology of gerontopsychopharmacological agents,* Ch. 11, pp. 461–492. In: F. Hoffmeister, G. Stille (Eds.), *Psychotropic Agents*, vol. 55, Part II*,* Springer, Berlin, DE, **1981**;

– *Le vieillissement cérébral: normal et réussi, le défi du XXIe siècle. Psychologie et sciences humaines*, P. Mardaga, Bruxelles, BE, **1993**.

The scientific, medical and therapeutic progress, Giurgea "brand" conducted globally is demonstrated by:

– development from *Piracetam* (DCI)/ *Nootropil*® UCB-Pharma of a new class of neurotropic and psychotropic drugs – *Racetams (Aniracetam, Oxiracetam, Pramiracetam, Nebracetam, Nefiracetam* etc.);

– maximum diversification (concentrations, pharmaceutical forms, bioavailability and routes of administration) of piracetam and related products;

– expansion of the pharmaceutical industry of Racetams on all continents, and

– the fact that, UCB-Pharma, Belgium became in **2006** a *Global Biopharma Leader.*

In addition, the author paternity of Giurgea nootropic therapy is also corrected (by the contribution of **drs. Riga team**). Romanian author:

– wordpress.com/nootropic;

– nationmaster.com/encyclopedia/nootropic;

– psychology.wikia.com/wiki/nootropic.

6. The group formed by Corneliu Oniscu, Ştefan Cilianu, Dumitru Dobrescu (Romania) conducted an interdisciplinary (chemistry, pharmacy and medicine) and multicentric scientific cooperation (Iasi, Bucharest/2 universities and one research institute). This has led to the development, between **1985–1995**, of the drug *Meclosulfonat* (DCI)/*Romener*® Sintofarm SA:

– C. Oniscu, *Chemistry and Technology of Drugs. Meclosulfonate,* pp. 264–268, Technique Press, Bucharest, **1988**;

– D. Dobrescu (Ed.), *Romener*®*. Genuine Romanian Drug. Psychoenergizer and Anti-convulsive. Preclinical Studies*, ICCF and Sintofarm S.A., Bucharest, **1993**;

– Sintofarm S.A. and ICCF Bucharest, Romener® Symposium, *Genuine Romanian Drug. Psychoenergizer and Anticonvulsive. Experimental Pharmacological Researches and Clinical Studies*, Bucharest, June 25, **1993**.

ASFA – neurotropic – psychotrop – somatotrop drug (first generation) is a 4-sulfon amido phenoxy acetic acid. *Meclosulfonate* (second generation) is an ester hydrolyzing in 2 pharmaco-therapeutic substances:

- an amino alcohol – *di methyl amino ethanol* (DMAE): antioxidant, metabolic precursor of choline (TMAE), acethyl choline and phospholipids, orthomolecular/nutriceutic drug;
- an acid – *2-chlorine-4-dimethyl-amido sulfonyl-phenoxy acetic acid.*

Meclosulfonate (Romener®) is a psycho-energizer (superior to Meclofenoxate) and anti-convulsive (similar to trimetadione), with anti-depressive actions, anti-hipertensive adrenergic, anti-cataleptic, antiemetic and analgesic moderate effects. Meclosulfonate is without acute (2 times lower confronted by Meclofenoxate) and chronic toxicity, without mutagenic, teratological and oncogenic activities, and without immune reactions (immediate and belated).

7. Dan and Sorin Riga team (Romania) has created in a transcausality strategy/disciplinarity *an anti-stress, anti-impairment, anti-aging and anti-pathogenesis therapy (Antagonic-Stress® class of drugs)*. Through *transcausalitaty*, *a specific* therapy has been created (causal, etio-pathogenic), *simultaneous* (from metabolic level to systemic intervention) and *synergistic* (of therapeutic augmentation and multiple cascade adjustments). *Transdisciplinarity* has included theoretical, experimental, preclinical, clinical, paraclinical, pharmacological, translational researches and studies, as well as the drug industry and multiple protection – registration, brand, patent inventions (national and international)[20].

Antagonic-Stress® acts through 5 classes of active principles: anti-oxidative and catabolic stress, anti-anabolic stress, vasodilator-normo-lipidemiant, energoactive and antitoxic/bio-trofic. It is an orthomolecular, homeostasis and adapto-genic, for prevention, protection, treatment and recovery therapy, for both genders, on all periods of life from young to old[27,30].

The scientific (bio-medical, therapeutic) and technological progress (pharmaceutical, high-tech technologies) were demonstrated internationally and multidisciplinary – selection:

– **1994 – 2005** global patenting: 27 patents, 2 patent international organizations (WIPO/ OMPI – PCT and EPO – Eur. Pat.), 25 countries (all G8), 5 continents / 17 European patents and 8 multi-national (US, CA, RU, JP, CN, KR, AU and BR Pats.);

– Gold Medal, Diploma with congratulations of the international jury at the Traditional International Exhibition Inventions – *Geneva Invention* **2013**;

– basic (**from 1974**)[28] and research & development studies (**from 1990**) are being cited in over 70 international treaties[3,18,43,46] of neuroscience and aging bio-medicine (mostly American), over 80 different titles of international biomedical journals[14], are selected by NASA library/ IDB, USA (**1994–2010**), are references in international programs of neurosciences[16] (**2012**) and American (**2009–2015**), are ranked No. 1 in the world TOP 20 – *Orthomolecular therapy* (**2004–2009**), and in the top 10 international works of *anti-aging medicine* (**2004–2015**).

TRANSDICIPLINARITY OF TIME RESEARCH IN BIO-MEDICINE

HEALTH-LOGENVITY MEDICINE

Epistemology, heuristic and synergistic progresses in the 4 fields define biomedical time based on transdisciplinary[24] *science/health-longevity medicine*[1,4,7]. Below are the analysis and synthesis, means / resources and objectives / goals, results and perspectives (developed in the last decade and a half), which substantiated and characterized the *health-longevity medicine*[12,31].

- **2003** – D. Riga, *SENS acquires SENSe: present and future anti-aging strategies,* Journal of Anti-Aging Medicine, vol. 6. no. 3, pp. 231–236, **2003**:
  A.D.N.J. de Grey vision[5] – *Strategies for Engineered Negligible Senescence (SENS) and the evolution of the sciences of aging* – longevity are being reported in the following chapters: *Real aging reversal strategies, Aging prevention and deceleration strategies, Tissue engineering – Regenerative medicine strategies, Elucidation of aging mechanisms, Epidemiology, demography and ethics*;
- **2006** – P. Derevenco, *Romanian scientific progress in international stress research and stress-aging medicine*, Fiziologia-Physio-logy, vol. 16, no. 1, pp. 9–14, **2006**:
  Background, Advances in stress medicine and stress research, New Romanian concepts in stress-aging bio-medicine, Romanian progress

in stress-aging research, bio-medicine and therapeutics, Validness of Romanian progress in the international scientific world, Conclusions and final remarks. Prospects;

- **2010** – S. Riga, D. Riga *et al*., *Longevity health sciences and mental health as a future medicine*, pp. 184–187. In: R. M. Tanguay (Ed.), Aging, Cancer, and Age-Related Diseases. Common Mechanisms?, Wiley-Blackwell-New York Academy of Sciences, Boston, MA, **2010**:
  Introduction, Global strategy of health concept, Longevity health sciences and mental health, Principles and strategies, Conclusions[33];
- **2011** – D. Riga, S. Riga, *The Science of Ageing – Global Progress*, Rejuvenation Research, vol. 14, no. 5, pp. 573–577, **2011**:
  Important meeting events, Meeting topics, Present and future directions of aging research and biogerontology, Basic and fundamental molecular and cellular mechanisms of aging processes, Immune system in aging, immune risk profile and experimental and medical immunological research, Werner syndrome, Fundamental mechanisms of brain aging and its connection with neuropathology (as part of neurosciences), Muscle aging, Proteomage Session, Exceptional longevity, Nutrition, nutrigenomics, calorie restriction mimetics[34];
- **2012** – D. Riga, S. Riga *et al*., *Health-longevity medicine in the global world,* Ch. 17, pp. 347–366. In: J. Maddock (Ed.), Public Health – Methodology, Environmental and System Issues, InTech – Open Access Publ., Rijeka, Croația and Shanghai, China, **2012**:
  Introduction (Health in ontogenesis; Objectives for health-longevity medicine. Past, present and future), Health and preventive medicine in ancient times (Prophylaxis and physical activity in traditional Chinese medicine; Preventive medicine in Greek and Roman antiquity), *From health to disease (Stress bio-medicine; Antagonism of health construction versus human pathology; Dynamic structure of destructive cascade; Risk factors and preclinical stages of aging and disease), Construction of human health-longevity (Longevity health sciences and mental health. Common characteristics; From health to health-longevity; Palaestric civilization; Declaration of Olympia 1996 on nutrition and fitness; New conception – strategy – therapeutics in pro-longevity medicine), Health-longevity strategy (Quality of life for all. The WHO public health policy; Health ↔ longevity tetrad; New health-longevity strategy. Structure of health as a pyramid; Health-longevity – a global progress), Conclusions*[35].

MARKERS OF BIOLOGIC TIME

The passage of time (duration, temporal periods) leaves its mark on all structural and functional levels of the body:

– longevity genes and gene manifested phenotypically by vulnerabilities;

– molecules, macromolecules, control and adjustment factors;

– subcellular, cellular and tissue functional structures, fixed and mobile;

– organs, systems and apparata.

Human senescence is a complicated and heterogeneous process with high regional and zonal specificity and individuality.

Crossing throughout ontogenesis determines:

– decrease of vitality and biological redundancy;

– increase of vulnerability and frailty of the elderly[42];

– increase in number, intensity and frequency of distressors (stress system, stress bio-medicine)[39,40];

– continuous and cumulated action of stressors, from oxidative-inflammatory stress, inflamm-aging stress to psychic stress (Fig. 4)[41,45];

– senescence (normal aging) and the frailty syndrome of the elderly;

– senility (pathological aging) and co-morbidities[44].

Footprint (marker, seal, hallmark) of biologic time is particularly evident in the non-dividing cells during ontogeny of the nervous system and the muscular system (neurons and muscle cells), and it is represented by lipopigments (LPs) – lipofuscin and ceroid[43,47].

Lipofuscin is the basic feature of cellular senescence, as ceroid is the accumulation product of aggressive external (environmental) and/or intrinsic (mainly genetic) factors. Together they are the main marker of brain vulnerability, distress, aging (senescence) and connected pathology (Fig. 4). Brain lipopigments storages are present in all types of neurons and also in glial populations (astrocytes, microglia, oligodendrocytes and pericapillary glia), (Figs. 5–8)[11, 47].

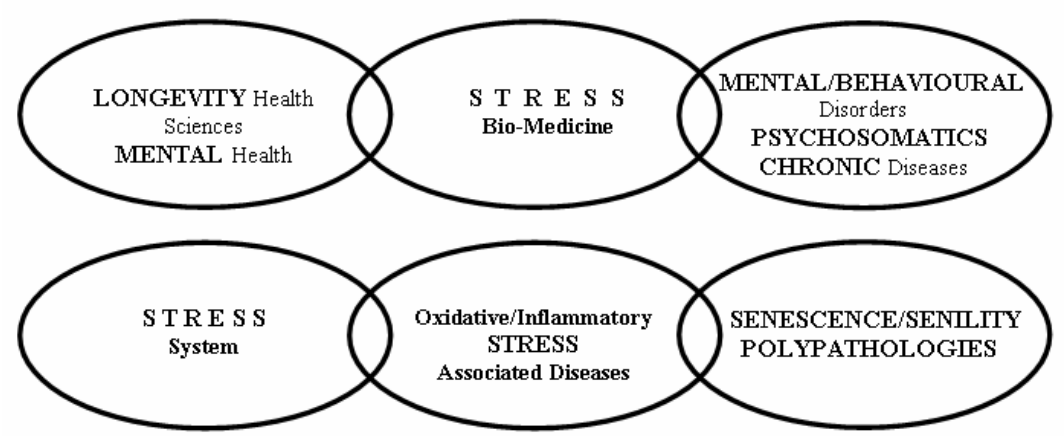

Fig. 4. Oxidative stress in stress bio-medicine, health, aging (normal, pathological) and diseases.

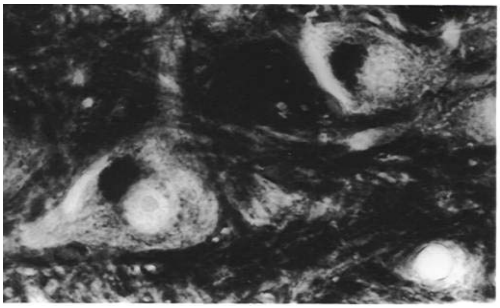

Fig. 5. Old rat (26.6 months). Brain. Pontine reticular formation. Light microscopy (Sudan black B). Large masses of neuronal LPs, gathered into perinuclear-unipolar clusters. × 900.

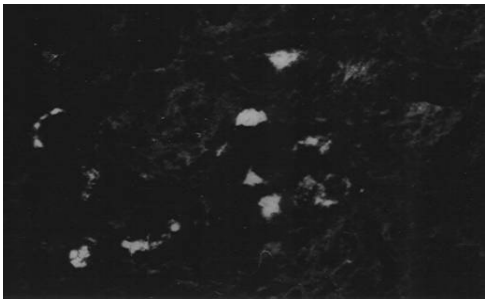

Fig. 6. Old rat (26.6 months). Brain. Pontine reticular formation. Fluorescence microscopy (Auto-fluorescence). Extensive perinuclear, uni- and bipolar accumulations of neuronal and glial LPs. × 650.

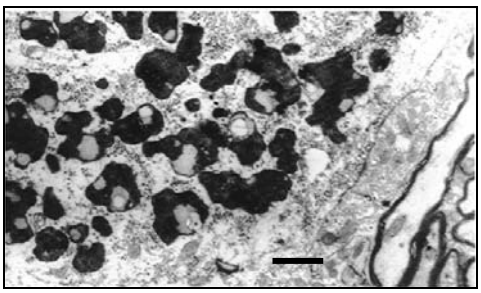

Fig. 7. Old rat (26.6 months). Brain. Cerebral cortex. Pyramidal neuron. Electron microscopy. Numerous polycyclic conglomerates of LPs, tend to cluster and to occupy a wide surface of the neuroplasm. Bar: 0.5 μm.

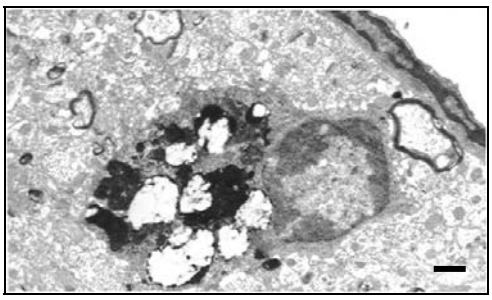

Fig. 8. Old rat (26.6 months). Brain. Hippocampus. CA3 field. Pyramidal cell layer. Electron microscopy. The microglia filled with subcellular garbage (which continue the vacuolation process) migrates towards the vascular pole of the neuropil. Bar: 0.5 μm.

Figs. 5–8 point out lipopigments (LPs) – lipofuscin and ceroid – neurobiological markers of oxidative stress and normal / pathological aging in animal brain, which are emphasize by light microscopy (cyto-chemistry), fluorescence and electron microscopy.

Glial system plays an important role in collecting of neuronal lipofuscin and ceroid. Owing to their transporting properties, and migration capacity of microglia, glial cells deposit the lipopigment clusters in pericapillary areas (Fig. 8).

This subcellular garbage can be therapeutically processed, reduced and discharged in endothelial cells and capillary lumen.

They constantly coexist and are correlated significantly with important changes in nerve cell biochemistry and structure[47]. Morphological impairments consist in diminution in number and surface/volume of polyribosomes and rough endoplasmic reticula, increase of defective (giant) mitochondria with a low rate of their degradation, decrease of normal mitochondria number and area, proteasome (multicatalytic proteinase complexes) instability and inhibition, deficient and poor function of cellular recycling systems, appearance and development of cytoskeleton abnormalities and amyloid deposits, induction of apoptosis (premature started, activated and/or accelerated). They are associated with neuronal loss, decrease in the surface/volume of neurosoma, dendritic aberrations, simplifications and destructions, axonal enlargements to meganeurites, considerably reduction of cortical myelin, and synapses loss[21].

Critical lipopigment concentrations generate cascades of negative lifelong subcellular events, and indirect, determine characteristic neuro-pathological aging profiles. Specific and associative negative neuropathologic consequences of lipopigment storages have multiple and detrimental impacts on neuron and glia homeostasis, from neuronal function to central nervous system physiology.

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