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Homeostasis: metabolic ways and regulation. New insight and new drugs

CONTENTS

PREFACE

Contemporary medical science is plunged into a deep system crisis stipulated by the discrepancy between the observed effects and basic theoretical constructions. This statements concerns pharmacology as well: the increasing value of creating new medicines by several digits, the uncontrolled growth of side effects and, as a result, the decreasing efficiency and simultaneous advance in price for medicines and medical services.

One of the ways to overcome the crisis is the retrospective analysis of former theoretical knowledge, which was either wrongly interpreted or simply forgotten, by using the modern research apparatus on the cellular and molecular level. The new vision of the world and the new science ideology are being developed by WWMA AG scientists on the basis of fundamental principles discovered in the past, and the knowledge of natural phenomena obtained with modern scientific technologies.

INTRODUCTION

The analysis of conceptions formed in the spheres of ancient naturopathic, occidental symptomatic and modern high-tech medicine, involving fundamental approaches in physics, chemistry, mathematics, permitted the authors to carry out a purposeful search of pharmacological products and their doses causing the optimal effect on human system.

Defining the creation of a principal new generation of methods and medicines for efficient provision of human vital functions as the goal of developments, we explored the basic mechanisms of metabolic processes and functional activity of human system cells on the atomic and molecular levels, which allowed to work out a number of fundamental discoveries:

- **the lipidic theory of human system aging is developed;**
- **a scheme of metabolic processes is created, which allows to reveal the mechanisms of maintenance of the energetic and biological homeostasis of all systems in a "universal" (non-specific) human system cell;**
- **methods and diagnosticums are developed for defining biochemical and pharmacological activity of natural and synthetic substances in nanodoses, besides:**
- *key metabolites are distinguished, which are markers of pathologies and aging and characterize the state of biochemical processes in tissues, organs and their systems on the human system level;*
- *brands of medicines are created, which have a generalized (immunomodulating, regenerating) and specific (prophylactic) effect on the human system* and are intended for curing the following diseases:

- diseases associated with metabolic syndrome;
- infectious diseases of bacterial, viral and fungous etiology;
- oncologic diseases of various etiology;
- neurodegenerative diseases: dementia, Parkinson's disease, Alzheimer's disease, etc.

With the help of these medicines and methods, a mechanism of regulating the whole set of intra- and intercellular vital functions is created, which consequently manages the homeostasis of separate systems and the whole biological organism.

The designed brands of medicines possess an unprecedented *pharmacological and physiological efficiency which restores homeostasis to the optimal level at any period of ontogenesis, taking into account all the phenotypic changes* at the moment of cure. Due to supra-minor doses of active substances in an isotonic solution, these medicines *have no negative side effect* on the human system.

Taken following thesis as the basic: **"Active longevity means an assured absence of oncologic diseases and efficient prophylaxis of metabolic and infectious diseases"** – the WWMA AG scientists elaborated a **system of measures** including medications and the methods of their use that allows under control **to guarantee active longevity till 90-100 years old to everybody** without hard and chronic diseases.

The main goal of research was the study of basic mechanisms of metabolic processes and functional activity of human system cells, which permitted to make a number of principal and fundamental discoveries, further used for creation of medicines and methods.

We suggest a methodological approach to description of metabolic processes in a cell, which takes into consideration

the biochemical evolution of living organisms since the appearance on the Earth of the first living form (methanotrophic bacterium).

The functioning of a biological system (cell, organism) is based on maintenance of its energetic and biochemical homeostasis. The development of pathologic processes and aging of an organism are connected with homeostasis violation or change.

METABOLIC SCHEME OF A UNIVERSAL HUMAN CELL

The metabolic scheme designed by WWMA specialists (Scheme 4) allows to distinguish the main junctions of metabolic ways, by which the connection of electronic and protonic flows is performed and main physiological functions are controlled, such as energy consumption and expenditure, synthesis of biological macromolecules, proliferation and apoptosis.

Glutathione is an important regulator of redox potential, protonic flows, in particular, being able to give and accept hydrogen ions. It restores oxidized compounds either immediately or together with glutathionreductase. After giving protons, glutathione is regenerated by interaction with NADP, which is formed in the pentose-phosphatic way of glucose oxidation. The reduction of NADP takes place during alpha-oxidation of long-chain fatty acids in peroxisomes, as well as during dehydrogenation of terminal fatty acids and olefins. Thus, protonic flows are formed during glucose metabolism (glucose-6-phosphate - pentose-phosphatic way). Free protons are used by the cell for fatty acids synthesis.

Glutathione is a tripeptide compounded of amino acids: glycocine, cysteine and glutamic acid. Metabolism of these three acids is closely interconnected with the participation of the fourth amino acid, serine. **Serine** is formed from **3-phposphoglycerate** (3PG) and **glutamic acid**, which are products of glucose oxidation: 3PG is a metabolite of glucose anaerobic oxidation, and glutamic acid is synthesized from the product of pyruvate, alpha-ketoglutatate acid. 3PG unites the ways of glucose metabolism in plasma with metabolic ways of fatty acids, which participate in the synthesis of all types of phospholipids and triglycerides (fat). On the stage of glutamic acid synthesis, metabolism involves NH_3 molecules and a number of amino acids is synthesized.

In the centre of one of the most important metabolic junctions which unites the serine and glutamine branches, the methyl group, CH_3, is located. The methyl group can be oxidized, forming a number of compounds of excessive chemical activity – formic aldehyde and formiate according to the chain “methyl group – methanol – formic aldehyde – formiate”. Together with ammonia oxidation, this way is one of the oldest metabolic acquisitions, as the primary atmosphere on the Earth was reduced and contained mostly ammonia and methane. Archaic methanotropic bacteria use methane as the only source of carbon and energy. The first forms of living matter already possessed the serine metabolic way, which became common for all cells. The base of life was metabolic ways united into a single structural and functional complex, involving molecules of ammonia, methyl groups, as well as formic aldehyde and formiate as products of methyl group oxidation. This metabolic junction is actually the regulator of basic metabolic flows and basic redox balance, i.e. the base of life. To stop life, the knot should be cut, but to prolong it, the knot should be “tied” correctly – in ontogenesis.

The system of methyl group transference controls such vital functions as proliferation, regulation of gene expression, signal transmission, regulation of enzymes activity. From serine, glycine is synthesized with the loss of one methyl group; glycine is dissociated with the formation of formic aldehyde, which controls its level in a cell. From serine, cysteine is also synthesized, involving the irreplaceable sulphur-containing acid – methionine. The sulphohydride methionine group is freed after detachment of one methyl group. Cysteine, glycine and glutamic acid form the glutathione tripeptide. Another methyl group producer is the metabolic way of cholesterol synthesis which takes place in peroxisome. At the final stage of cholesterol synthesis, three methyl groups are detached from lanosterol.

Methyl groups are used during phosphatydilcholine synthesis from phosphatydil serine (phosphatydil serine – phosphatydil ethanolamine – phosphatydilcholine). Together with cholesterol, phosphatydilcholine is the main component of cell membranes. The serine branch is also connected with sphingomyelin synthesis. The palmitic acid (saturated fatty acid $C_{16:0}$) when compounded with serine, sphyngosine is synthesized. When sphyngosine attaches another $C_{16:0}$ molecule, ceramide is synthesized, the immediate predecessor of shingomyeline. Thus, the serine branch is connected with fatty acid metabolism. In eukaryotic cells, from formiate, glycine and cysteine, purines are synthesized – adenine and guanine. Adenine is a part of transporting molecules transferring electrons, phosphate and methyl groups.

Functioning of cell metabolism is provided by maintenance of constant methyl group pool, which is controlled by the mechanism of their gradual oxidation according to the chain “developed” by methanotrophic bacteria: “methyl group – methanol – formic aldehyde – formiate”. As for eukaryotes, the oxidation of methyl groups is performed by enzymes which are

involved into the system of antioxidant defense, or detoxication, located in microsomes. This way of oxidation is so strictly regulated by eukaryotes that the excess of formic aldehyde and formiate causes immediate death, i.e. these compounds are virulent poisons. These metabolites perform excessively important functions, therefore their homeostasis is strictly regulated. Actually, this is the key metabolic and functional junction, the destruction of which causes immediate death. The second location of the "methyl group – methanol – formic aldehyde – formiate" way is in peroxisomes, where monocarbonic compounds are connected with catalase. This way is controlled by factors which regulate the activity and expression of catalase.

MARKERS OF PATHOLOGY

The scheme of cellular metabolic ways allows to distinguish the pathogenetic mechanisms by specific markers.

In the cytoplasm, the circulation of methyl groups takes place, which are transferred **by S-adenosylmethionine (SAM)** and **folic acid**. The change of SAM level accompanies the process of aging. The deficiency of folic acid causes demyelination of nerve fibers formed from phosphatidylcholine and sphingomyeline.

Homocysteine can be viewed as a marker of atherosclerosis with middle-aged and elderly people. Homocysteinemeia also indicates pathology of foetus development caused by the lack of folic acid in the mother's organism. Homocysteine attaches a methyl group with the involvement of vitamin B_{12}. Aging is characterized by homocysteinemeia, decrease of methionine and deficiency of vitamin B_{12}. The study of SAM function and the "methionine –

homocysteine" recycle is an object of gerontologists' attention at the moment.

The accumulation of **ceramide** in a cell cause the induction of apoptosis. Ceramide also controls tumour growth. In ceramides of tumour cells, the content of polyunsaturated fatty acids is increased. In the "apoptosis – proliferation" regulation zone, ceramide influences the speed of tissue aging and the loss of cell mass.

LIPIDIC THEORY OF HUMAN AGING

This theory is based on the point of view according to which human organism is a thermodynamic system based on fatty acid metabolism as an energy substrate.

Human life can be conventionally divided into several periods. A man is born with the heightened level of fatty acids in blood. During the first stage, which lasts up to 25 years (the growth period), the excess of fatty acid is spent on the growth of cell mass. At the same time, the level of fatty acids in girls' blood decreases slower than in boys' blood; i.e. sex differences are manifested on the earliest stage of life.

The second period of human life is *stationery*. The term does not only mean that the major part of physiological characteristics is stable, but also that it is marked by a definite level of energy consumption and expense. At this period, energy is spent on reproduction (women) and physical activity (men). The excess of fatty acids is accumulated in adipose tissue. As a result, the weight of adipose tissue steadily grows. Adipose tissue maintains the glucose homeostasis, being a "damper" where the excess of energetic substrates (glucose and fatty acids) is accumulated as fat.

By the end of the stationery period, the weight of adipose tissue reaches its physiological maximum. The excess of fatty acids and glucose in blood is no more compensated. The end of the stationery period is marked by the gradual growth of fatty acid level in blood. The actual reason of the increasing level of fatty acids in blood is obscure. As a result, homeostasis of energetic substrates and, as a consequence, the inner environment of the human system is changed. One of the adaptation mechanisms is fatty acids accumulation in non-adipose tissues and remodeling of the cardiovascular system.

The third period of ontogenesis is marked by dysfunction of adipose tissue and the fatty regeneration of non-adipose tissues, which causes system pathologies, such as atherosclerosis and 2^{nd} type diabetes mellitus. The complications of these diseases – stroke and myocardial infarction – are the main cause of death in late ontogenesis.

Metabolism of fatty acids is closely connected with reproduction. This connection is performed in blood flow at the junction of metabolic ways of cholesterol and triglycerides (Scheme 1). Triglycerides are secreted into blood by liver cells together with apoB-100 protein in the form of very low density lipoproteins (VLDL). Triglycerides are synthesized in liver with the involvement of free fatty acids which come there by the portal vein from abdominal visceral adipose tissue. In the blood flow, triglycerides in VLDL are hydrolyzed by the lipoprotein lipase with the formation of free fatty acids. The activity of lipoprotein lipase is controlled by adipose tissue. Free fatty acids are connected with albumin and transferred to somatic cells. In VLDL, triglycerides are gradually replaced by cholesterol ethers which come from high density lipoproteins (HDL) and are transformed into low density lipoproteins (LDL). HDL is the central point where metabolic ways of cholesterol in the blood flow are conjugated. HDL catches cholesterol from

membranes of somatic cells (Scheme 2). From the phosphatidylcholine fatty acid and the caught cholesterol, cholesterol ethers are synthesized in HDL. We distinguish two cycles of cholesterol recirculation in the blood flow. The first is free cholesterol transmission which is transferred by HDL to the liver, from the liver comes with bile into small intestine, is reabsorbed into blood and again compounded with HDL. The second is the transmission of polyunsaturated fatty acids into macrophages. Polyunsaturated fatty acids are transferred from HDL to LDL in the form of cholesterol ethers, and from LDL to macrophage. In a macrophage, cholesterol ethers are dissociated with the formation of free cholesterol and fatty acids. Fatty acid is used for inflammation mediator synthesis. Cholesterol is exposed on macrophage membrane, where it is caught by HDL. HDL also transfers cholesterol ethers into steroidogenic tissues, where steroid hormones (estradiol and testosterone) are synthesized from cholesterol. LDL transfer cholesterol ethers to liver, where fatty acids are synthesized from cholesterol. Capture of LDL by hepatocytes is performed by a specific receptor, the activity of which is regulated by estradiol. Bile is necessary for absorption of exogenous fat. The cycles of cholesterol recirculation in blood are controlled by non-specific receptors CD_{36} (macrophages) and scavenger receptor B_1 (liver and steroidogenic tissues). The only specific receptor (LDLr) is located on hepatocytes and controls the bile production. Bile is necessary for inflow of exogenous fat from small intestine into blood flow.

Sex differences are distinguished on LDL level. In female organism, LDL comes mostly to liver for bile production, in male organism, it comes to macrophages.

Age-associated growth of abdominal visceral adipose tissue causes the increase of free fatty acid flow into liver, increase of VLDL secretion into blood and triglyceride hydrolysis in VLDL, and, as a result, relative increase of free

fatty acids in blood and in pericellular space. The increased inflow of fatty acids into a cell violates its intracellular homeostasis, which causes elevation of membrane cholesterol (Scheme 3). The result of a higher VLDL secretion by liver and the quantity of membrane cholesterol is the increased LDL synthesis and the decrease of HDL cholesterol on condition that the LDL inflow into liver either remains stationery or lowers with the decrease of estradiol level. The consequence of redistribution in cholesterol cycles is the enhanced inflow of LDL into macrophages. The increase of triglyceride level and the decrease of cholesterol content in HDL is the first and key criterion in diagnosing the metabolic syndrome, a complex of symptoms caused by the growth of abdominal visceral adipose tissue mass. Metabolic syndrome, developing in the late ontogenesis, causes atherosclerosis and the 2nd type diabetes mellitus and death from stroke and infarction in elderly and old aged.

Liver, muscle and adipose tissues are united into a “metabolic triangle” which regulates the stationery glucose level in blood (Scheme 5). In these three organs, insulin receptors are located. Myocyte is the main consumer of energetic substrates – glucose and fatty acids. The lack of glucose in a muscle is compensated by protein dissociation with freeing of alanine amino acid. Alanine comes to liver where it initiates a new glucose synthesis (gluconeogenesis). The excessive glucose inflow into blood induces insulin secretion by pancreas, which directs its flows equally into the three organs. In adipose tissue, glucose is accumulated as fat. Adipose tissue segregates the leptin hormone, which controls beta-oxidation of fatty acids in muscle. Leptin and insulin form two competing flows – glucose and fatty acids. In case of fatty acid excess in blood, the insulin receptor is “turned off” and the glucose blood level increases. The “metabolic triangle” maintains the stationery glucose flow into neurons. Glucose

homeostasis violated, adaptive mechanisms in nerve tissue are initiated, which finally cause the neurodegenerative process and age dementia.

Fat metabolism is closely connected with water production. During the beta-oxidation of one palmitic acid molecule, 16 H_2O molecules, and during its synthesis, 6 H_2O molecules are segregated. Thus, adipose tissue participates in maintaining water-salt balance. It secretes the main components of renin-aldosterone-angiotensin system (RAAS): renin, angiotensins I&II, angiotensinogen, angiotensin-transforming enzyme. Their secretion depends directly on the size of adipose tissue. Its excessive weight can change the water-salt metabolism, to which RAAS reacts. RAAS is proved to play an important role in the development of the left ventricle hypertrophy. Connected with receptors to angiotensin I. angiotensin II causes a direct inotropic effect on the heart, which stipulates the increase of heart contractility, causes the growth and proliferation of cardiomyocytes, heart remodeling, ventricle hypertrophy and dilation. The elderly age is characterized by the increasing accumulation of fat in non-adipose tissues. It is typical for all people, including those with normal body weight index. A slight but prolonged change of water content in tissues induces an adaptive process in a cardiovascular system which contributes to myocardium remodeling even among practically healthy elderly persons. The body weight index increasing, myocardium remodeling is accompanied with vessel remodeling. Among elderly people, the frequency of atherosclerosis affection of common carotid artery increases with the growing graveness of arterial hypertension. Vessels contraction is an adaptive mechanism which prevents the collapse of vessel walls in case of high tension created by a higher liquid pressure in the bloodstream.

REGULATION OF INTRACELLULAR CHOLESTEROL HOMEOSTASIS

With the help of Scheme 4, the change of functioning of intracellular homeostatic system can be traced under the condition of an increased content of free fatty acids in the pericellular space. Regulation of cholesterol content in the cell membrane (Scheme 3) is connected with metabolism of methyl groups, which are formed during its synthesis in peroxisome from lanosterol and the formation of homocysteine from methionine. These methyl groups are spent on phosphatidylcholine synthesis. This maintains the balance between cholesterol and phosphatidylcholine formation, their relative content in the membrane being 1:1. The inflow of fatty acids into a cell increasing, the rate of glucose anaerobic oxidation grows, as well as the content of 3PG and serine, and cholesterol synthesis increases, which causes the growth of methyl group content. The increase of serine, 3PG and methyl group content causes the violation of balance between the synthesis of glutathione and phosphatidylcholine in the latter's favour. The consequence of the imbalance is the homocysteine accumulation.

The catalase system of methyl group oxidation (1) is regulated by various factors, including hormones (e.g. growth hormone). The microsome system of detoxication (2) reacts at the microconcentration of formic aldehyde, which in case of a higher concentration becomes a virulent poison. This system is regulated by glutathione, the synthesis of which depends on three amino acids – cysteine, glycocine and glutamic acid.

The activation of microsome system of detoxication with supra-minor doses of exogenous formic aldehyde normalizes the proportion of aerobic and anaerobic ways of glucose oxidation, increases the content of glutathione, decreases the homocysteine content and cholesterol synthesis. The

activation of detoxication system has two stages. On the first stage the non-toxic excess of formic aldehyde blocks the oxidation of methyl groups in microsomes, the increase of phosphatidylcholine and cholesterol synthesis, as well as homocysteinemeia. On the second stage, the glutathione synthesis grows, the methyl group oxidation increases.

Modulations of membrane cholesterol flow into the cholesterol pool circulation in blood cause changes in the LDL level. The prolonged effect of minor formic aldehyde doses gradually diminishes the LDL level.

REGULATION OF INTRACELLULAR HOMEOSTASIS DURING NEURODEGENERATIVE PROCESSES (ALZHEIMER'S DISEASE)

Scheme 4 also permits to track the changes in the functioning of intracellular homeostatic system under the condition of the increased glucose content in the neuron pericellular space (scheme 6).

With Alzheimer's disease the excess of glucose flowing into a cell is spent on the synthesis of ballast protein – beta-amyloid. The synthesis of amino acids is activated, the metabolic predecessor of which are the components of tricarbonic acid cycle and glutamic acid. Glutamate is the key metabolite in the synthesis of serine, serine-glycine, phosphatidylcholine and sphingomyeline. Glycine, glutamate and acetylcholine are the key metabolites which determine the normal functioning of neuron – the processes of stimulation, inhibition and transmission of nerve impulse. The metabolism of these three compounds is closely connected with metabolism of methyl groups, which are oxidized in the microsome system of detoxication. Glycine synthesis is

connected with the metabolism of methyl groups, and its catabolism with the formation of formic aldehyde. Thus, the functioning of neuron involves the detoxication system and methyl group transmitters, folic acid, in particular. With the synthesis of amyloid protein the expense of glucose as energetic substrate decreases, as well as the need in adenine as an ATP substrate. As a result, glycine catabolism grows, which blocks the methyl group oxidation. The balance between formation and oxidation of methyl groups is violated.

Supraminor doses of formic aldehyde prevent glycine catabolism, increase the adenine and glutathione synthesis, and restore the homeostasis of methyl groups and key substrates – glycine, glutamate and acetylcholine.

BRAND OF MEDICINES BASED ON NATURAL METABOLITES

Persistent efforts and systematic actions of the research team of the company WWMA AG and its subsidiaries in various countries within last 15 years have led to creation of drugs on the basis of natural metabolites of organism and synthesized substances in the very low doses dissolved in an isotonic solution. The main drugs with working names – PNM and GPI, passed preclinical researches (with agricultural and laboratory animals) and showed encouraging results, as in metabolism restoration at cellular level, and normalization and activation of general homeostasis of a whole body.

Thus, in the event of illness that is negatively realized at the cell metabolism level and significantly accelerates the processes of aging, this medication can be used (by specially developed techniques) not only as a preventive drug but also as a highly effective therapeutic drug. The medications are

effective in respect to infectious and inflammatory diseases, particularly for chronic recurrent infections, malignant neoplasms, primary and secondary immunodeficient conditions. It can be used for activation of own stem cells in cosmetology.

Summarizing all mentioned above of the PNM medication influence mechanisms at the cellular level it is possible to define a final result of the presented pharmacological medication effect as a shift of cells to the level of «young» functioning with all favourable results for the organism as a whole: healing, rejuvenation and prolonging life.

PNM has an influence upon the biochemical processes of oxidation inside the cell optimizing the ratio of intracellular processes of aerobic and anaerobic oxidation that are essential value in the aging processes realization, carcinogenesis, in the intracellular parasitism of pathogens and the inability to release the body as a whole from pathogens. During pathological aging an increase of triglycerides and of free fatty acids in the blood is observed. The excess of energetic substance such as fatty acids in the pericellular space results in their accumulation inside the cell. Thus, the Intracellular balance of oxidation of two major energetic substrates such as glucose and fatty acids breaks. This means that equilibration between aerobic and anaerobic oxidation branches changes (the same is in aging cell or in a cell damaged by viral agent, toxin, etc.). As a result the cell switches to a very unfavourable biochemical regimen, where the effectiveness of the oxidation processes reduces.

The fatty acid penetrating into the cell results in an intra-cellular accumulation of triglycerides which the cell is unable to recycle. Some part of fatty acids, particularly palmitic acid, and triglycerides are substrates for the synthesis of membrane phospholipids. Palmitic acid synthesizes a

sphingomyelin which has a great affinity to cholesterol. Palmitic acid, cholesterol and sphingomyelin constitute the membranous «rafts» to which the receptors are anchored. Rafts stiffening leads to receptors deactivation and the cell become «occlusive» to external signals. Thus the «devolution» of cell membranes (a kind of sclerosis or aging) is observed. «Walled-up in callous fat" cell lives as provided on its own because of losing the ability to perceive environmental signals. A damaged membrane cell ceases to adequately respond to both the signals from its own environment as well as the impulses from the regulation centres (nerves, endocrine systems et ct). Violation of the receptors function and metabolic disbalance are an initial stage of cascade homeostasis and systemic changes that eventually lead to many «diseases of aging» (hypertensive disease, ischemic heart disease, diabetes, etc.) and to immune-related disorders. When the fatty acids excessively flow into a cell they disrupt the utilization of carbohydrates and insulin receptor becomes «disconnected». Insulin resistance leads to the failure of glucose homeostasis and the content of glucose in the blood increases (the formation of diabetes mellitus) and its toxic and highly carcinogenic metabolites (glucose toxicity) also accelerate the aging process in general. Thus if the membrane receptors cease to respond to the hormone-insulin then diabetes develops, if the receptors do not interact with the receptors of cells that are responsible for immunity then the cancer may be in progress, etc.

The cells are trying to cope with the glut «bad lipids» by their reactive oxygen species direct oxidation. However, during the lipid peroxidation the accumulation of toxic and corrosive products occurs that are lipid peroxide. The content of fats in the blood and elevation of oxidative reactions producing oxygen reactive species also leads to accumulation of lipid metabolism products in the vascular walls, to the

atherosclerosis development accompanied by inflammation and increased thrombogenesis, and as consequence it leads to aging processes acceleration.

PNM treatment creates the conditions for the optimization and stability of the oxidative processes balance in the cell, for its active division and operation. During such «rejuvenation» there is enough energy produced in the cell (as ATP), a transit of substances into the cell and removal of cellular debrises more effectively performed, i.e. a full detoxification restored at the cellular level, the structural elements of cells are actively synthesized and «digest» the unwanted elements, including alien pathogens (viruses), a viral infection carrier state goes on into elimination stage.

Under the influence of PNM an optimization of aerobic-anaerobic oxidation processes and the proper functioning of lipid peroxidation in the cell are taking place. **As a result all functions of membranes are restored:**

- **maintenance of the correct** substances gradient both inside and outside the cell, creation of a sufficient biopotential on the membrane-level. There are no prerequisites for the kinds of «aging diseases» development, related to the violation of the cells permeability (arterial hypertension, etc.)
- **proper functioning** of core micropores provides an adequate penetration of the substances involved in protection, DNA synthesis and the withdrawal of substances that threaten DNA to be damaged. Hence, mutation process of genes (oncology products) decreases
- **proper functioning** of the structural components of membranes (protein-receptor, carrier protein, protein-enzymes) ensures the normal functioning of cells (the absence of reasons for the atherosclerosis

development, diabetes mellitus, endocrine diseases, etc.)
- **adequate recognition** of damaged cells and start-up of apoptosis processes (full protection against external pathogens - antiviral effect, early detection and eradication of oncology cells)
- **through impact** on CD4 - receptors for HIV prevention

Effecting in phagocytosis, as an universal method of «rejuvenation and protection» for intracellular and organism level. Due to effects on membrane structure and the creation of sufficient energy reserves in the cell there are created unique conditions for **the complete phagocytosis.** By virtue of it there is decomposition of unwanted intracellular and infectious agents to the simple substances (without the formation of residual compound products), that falls into reutilization. There is no «pigments aging» accumulating in the cells such as sediment undigested structures, the cells are functioning of full value and able to get rid of the viral load.

Influence on the stem cells with stimulation of their own stem cells production, namely cells of the spleen and red bone marrow and liver. At the tissue and organ level, this effect appears as proliferative and regenerative processes increase (e.g., proliferation of bone marrow cells increased in 13.5 times, cells of the spleen - in 4,5 times).

Effect in the immune processes. Immunotropic activity valuation suggests that the medication effective on all links of specific immunity and nonspecific resistance of an organism at all levels.

- **stimulates** the production of alpha and beta-interferons
- **mobilizes and activates** macrophages (phagocytosis enhances the absorption phase, increases the number

of phagocytes, enhances the migration of macrophages), while not affecting their viability

- **limits** the formulation of inflammatory cytokines (interleukins 1,6,8, TNF – tumour necrosis factor)
- **having in possession of strong immune-activating** effect by increasing the creation of anti-body-creation cells and production of antibodies to antigens of different nature. Due to interaction with antigens, allows to immune protection cells fully recognize a complete foreign agent and provide a high immune response. Similarly to it the positive results achieved in the therapy of hormonal and nervous systems disorders, caused by emotional stress with the formation of bacterial heat shock proteins, which are under the influence of PNM are successfully eliminated
- **inhibits** the viruses replication
- **increases** the organism's resistance to infections caused by viruses, bacteria or fungus disease. There is evidence for the anti-oncology effects of the medication

In HIV-infected it reduces the concentration of HIV in blood cells and plasma, activates the immune response, prevents the development of opportunistic infections. It is effective in treatment of recurrent infections mucous and skin caused by fungal agents. Stimulates antigen-specific inductive phase of immune response, at the same time increasing production of cytokines and immune cells achieving a productive phase of immune response to the elimination of antigen development. Enhances formed mechanisms of immune response. Reduces the severity of non-specific antigen reactions including anti-inflammatory reactions that are caused by TNF (by interleukin 1, and others).

The influence on the apoptosis processes – a special mechanism of self-destruction of damaged or aging cells, which is also realised during the organisms fight with the infectious diseases (such as AIDS, hepatitis, etc., also oncology disease).

The result of many virus attacks and oncology mutations is inhibition of apoptosis at which point a cell attacked by virus does not die, but realises all of its pathogenic effects, and oncology cells become virtually «immortal». As a result of PNM medication effect at the cellular level (by reducing the level of transforming growth factor), the process of apoptosis functions are restored (a universal mechanism for the organism protection). Due to this to apoptosis are exposed not only abnormal cells of the vascular wall, but the abnormal cells of other tissues such as liver, thyroid gland, adrenal glands. An organism's cleanup of pathogens and oncologic focuses occurs. As a result, the function of organs is restored, including the activity of enzymes strength that guarantee the cleavage of lipids, physical and chemical condition of the blood proteins is normalized, which ultimately leads to the normalization of blood cholesterol levels. Also it was found out that PNM effectively suppresses development of tumour cells colonies in cell and tissue cultures (27 stocks were investigated).

PNM effect:

1. **Optimizes** the processes of lipid peroxidation;;
2. Activates NO synthase:
   - **Normalizes Ca-homeostasis**;
   - Prevents the aggregation of **thrombocytes;**
   - Reduces adhesion **of neutrofils to endothelium.**

Normalization of oxidative system of a human body by the created drugs leads to restoring physiological balance.

At the moment results of the first phase of clinical investigations are summed up and are set below**:**

- The drugs have low, but stable diuretic and cholesterin regulating action what allowed to lower to all examinees and stabilize (at 45%) arterial pressure at the level close to norm of younger patients (see illustration 1)
- Application of drugs within the limits of the techniques developed by us leads to reduction of oxidative system activity and amount of lipid peroxides in blood
- Independent diagnostics confirms serious decrease of stenosis of blood vessels (cardiovascular system): 27% of patients stenosis decrease from 18 % to 32%
- As general indicators of patients condition by examination in three weeks after end of clinical researches are established: shortness of breath decrease, improvement of blood supply of brain vessels, general increase of immune stability to infectious diseases.

MEDICINES DEVELOPED BY WWMA AG

Today, the following medicines are patented and have passed the stage of preclinical testing:

Patent application title:
Cholesterol Regulating tools (XR)

Cholesterol regulating medicine containing an active component of chemical origin and a target additive is

distinguished by containing water solution of 36.5-40%-formic aldehyde as active component and a 0.85-0/95% isotonic solution of sodium chloride for injections.

Patent application title:
Stem Cells activation (SCA)

Medicine for activation of the stem cells, the containing active beginning of a chemical origin and a solution of chloride of sodium for the injections, different that as the active beginning it contains formic aldehyde at a following parity of components, weights. %:
Formic aldehyde 0,00003-0,004
Solution of chloride of sodium for injections of 0,85-0,95 % of concentration - the rest

Patent application title:
Cytostatic Composition (XR-ONCO)

A cytostatic composition comprising an effective amount of an aldehyde in a pharmacological salt solution is shown to be effective at inhibiting growth of a number of cancerous cell lines.

According to a first aspect of the invention, there is provided a pharmaceutical composition comprising: an aldehyde suspended in a solution of a pharmaceutically acceptable salt in water. That is, there is provided a pharmaceutical composition comprising: an aldehyde suspended in an aqueous solution of a pharmaceutically acceptable salt.

Patent application title:
Medicine normalizing Redox balance in human organs and tissues (GPI)

Medicine normalizing the redox processes in the human system containing a chlorine and sodium compound is distinguished by containing an extra component, the natural metabolite of Streptomyces globisporus/grudelus fungus, and sodium chloride for injection as a chlorine and sodium compound.

EPILOGUE

The above-mentioned discoveries of WWMA AG scientists have permitted to continue the research in the fundamental and applied spheres of human medicine in the following directions:

1. Development ***of mechanism of regulating the specific mitochondrial activity*** and its use for solving problems of infectious pathologies of bacterial and viral aetiology;
2. Development of ***mechanism of forming and launching a specific endogenous vaccine*** in the human system ***for curing bacterial infections*** and ***viral aetiology***;
3. Investigation of the mechanism of maternal chromosome heredity and its use ***to solve the problems of infectious and non-infectious diseases with the transmission of anti-infectious steadiness to the next generation in the maternal line*** on laboratory and domestic (swine, cattle) animals with further modeling of similar processes in the human system;
4. Modeling on laboratory and domestic animals the process of formation of an active ***T-killer system of immune defence during the neonatal period and its prolongation into the postnatal period in the phenotype***;
5. Development method and drugs to activate specific complete viruses phagocytosis and other endocellular pathogens for elimination of viral etiology infection, including flue, herpes and chlamydia;
6. Theoretical foundation and reception of experimental results in the framework of ***development of transferring specific antibodies inside oncogenic***

cells (know how), development of a complex approach to prevention and cure of oncologic diseases; organization of industrial production of medicines for efficient ***cure of oncologic diseases of various aetiologies, including the 3rd and 4th stages*** (before the development of ascites process);

7. Development of drugs and methods for reproductive capacity recovery is an innovative approach in sterility problem solution.
8. Activation method development for mycobacteria and brucella complete phagocytosis according to stages: stage 1- base protein fractions detection in relation to tuberculosis mycobacteria, stage 2- phagocytosis type detection in lab animals, stage 3- mycobacteria elimination process simulation in farm animals– Heavy beasts; to develop drugs series for human tuberculosis treatment based on this methods;
9. Studying complex of questions concerning development of a metabolic syndrome – basis of age-associated diseases and aging of human system:
    - Etiology of metabolic syndrome;
    - Diagnostics of metabolic syndrome;
    - Regional distribution of adipose tissue and metabolic syndrome in late ontogenesis;
    - Age-related changes of metabolism in pathogenesis of late ontogenesis diseases;
    - Age-depending pathologies as a consequence of adaption to phenotypic changes of the inner environment of the human system;
    - Metabolic syndrome, obesity, fatty hepatosis;

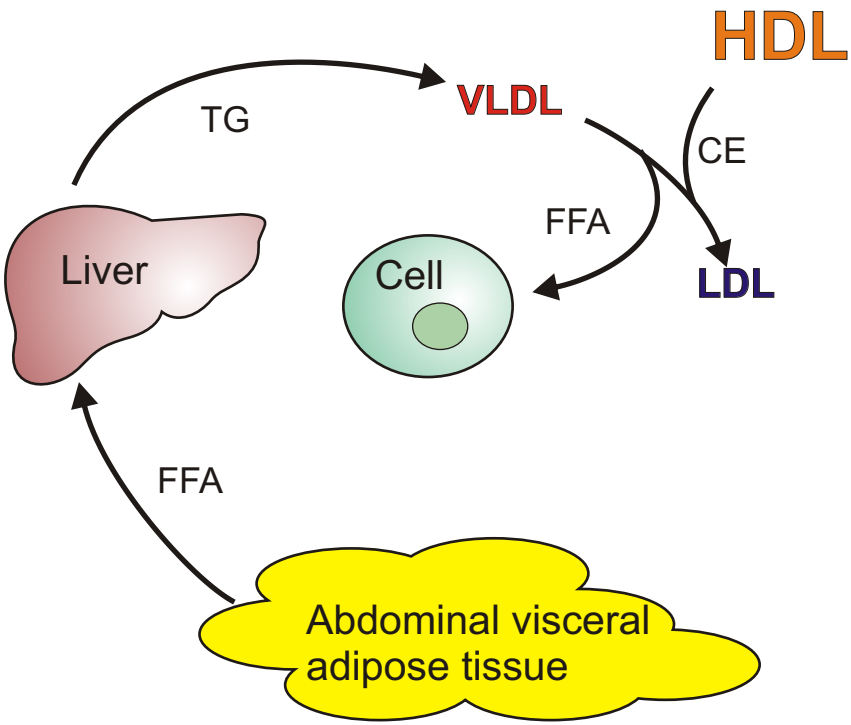
- Free fatty acids as a marker of age-related changes of homeostasis and aging;

- Age-related changes of energy metabolism, diseases in late ontogenesis and aging;
- Metabolic ways on the cellular level and markers of age-associated pathologies and aging;

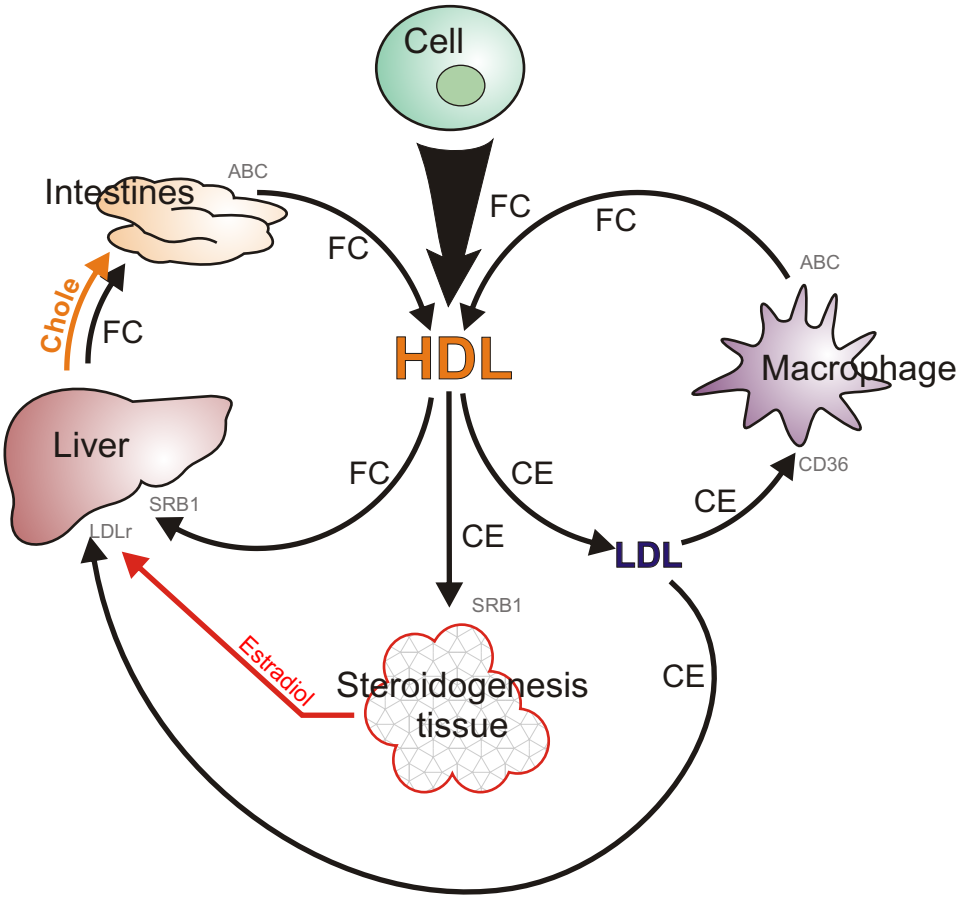
- Aging of human body as a system process, perspective lines of pharmacological medicines for curing age-associated diseases and new geroprotectors.

10. Development on the base of the above-mentioned research of a principally new generation of geroprotectors;

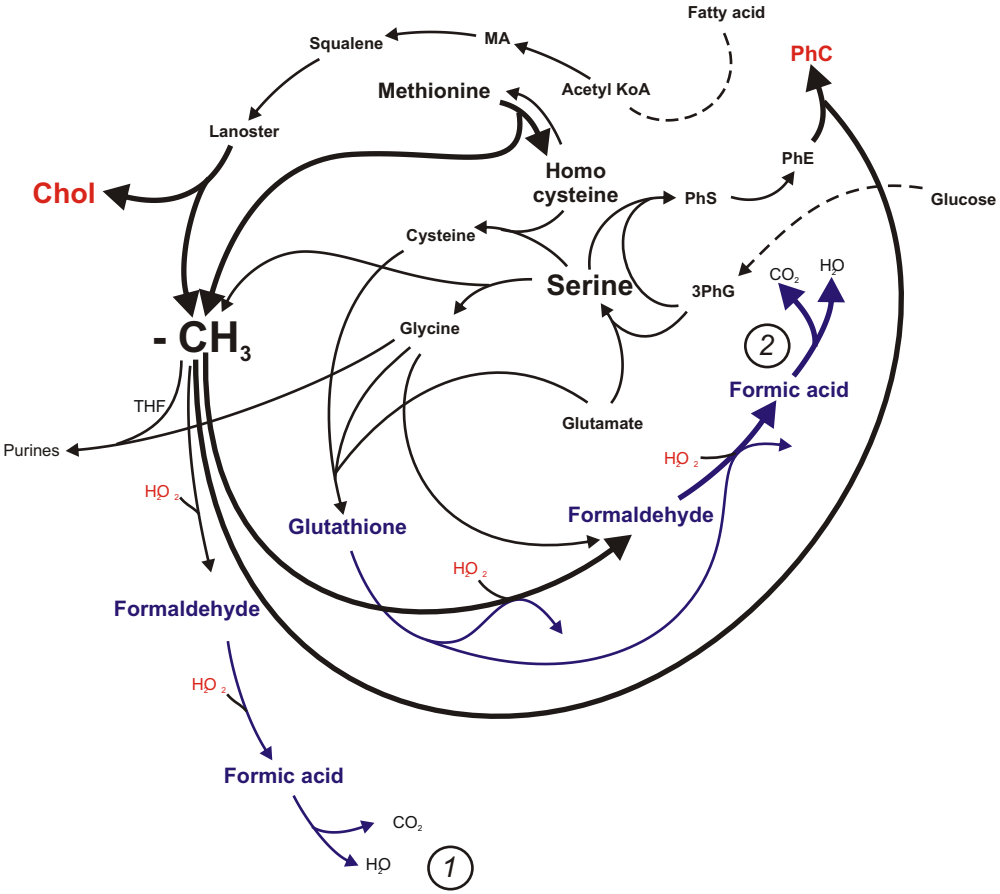
The creative team of scientists from the holding company headed by WWMA AG achieves the defined goals, being guided by the motto suggested by the well-known scientist Claude Bernard: "**When the counter fact is contrary to recognized theory, so it is necessary to recognize the fact and reject the theory if even this theory supported by great names is accepted by all.".** We added our thesis to this thesis: "**The counter fact is to be verified objectively, adequately and repeated in any conditions".**



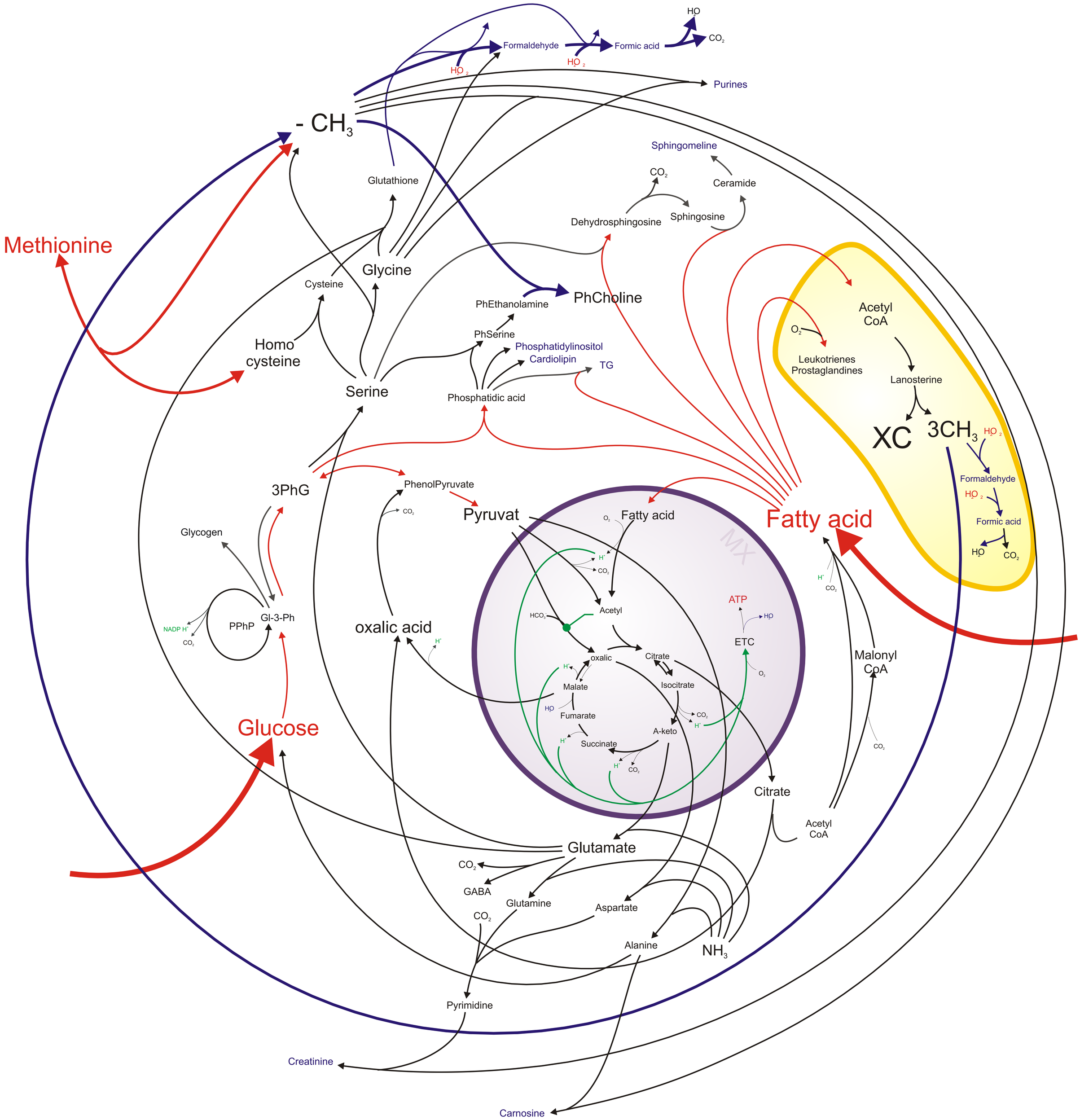
Scheme 1. Crossing of metabolic ways of the triglycerides and cholesterol in blood



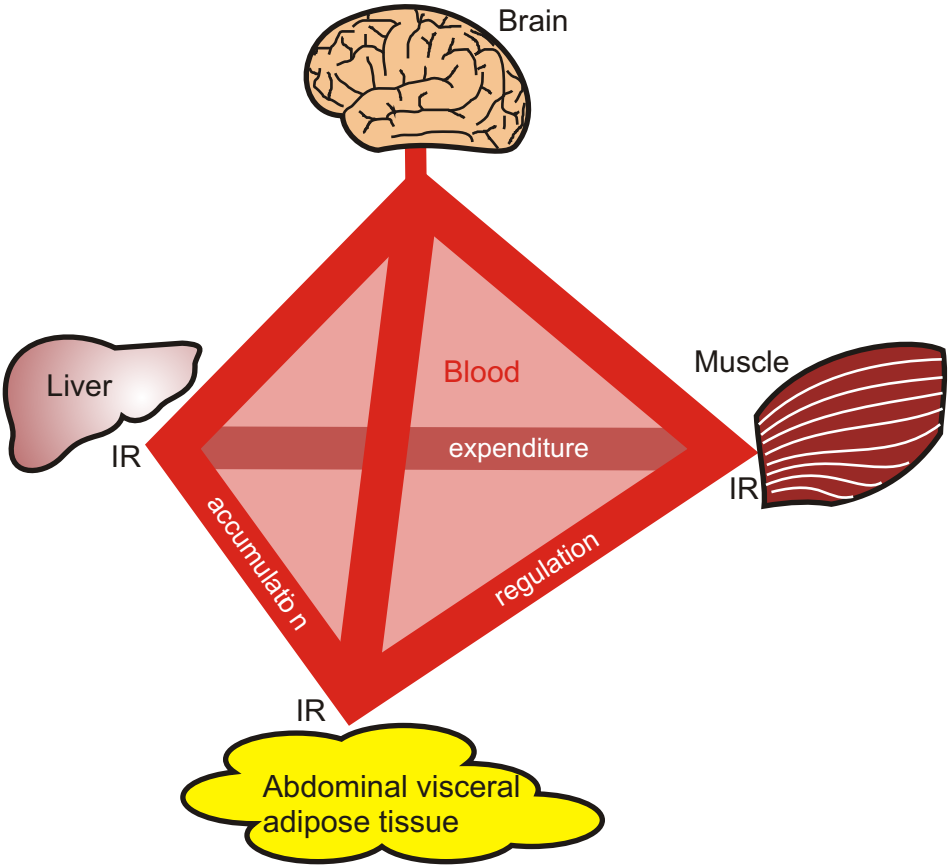
Scheme 2. Cholesterol recirculation system



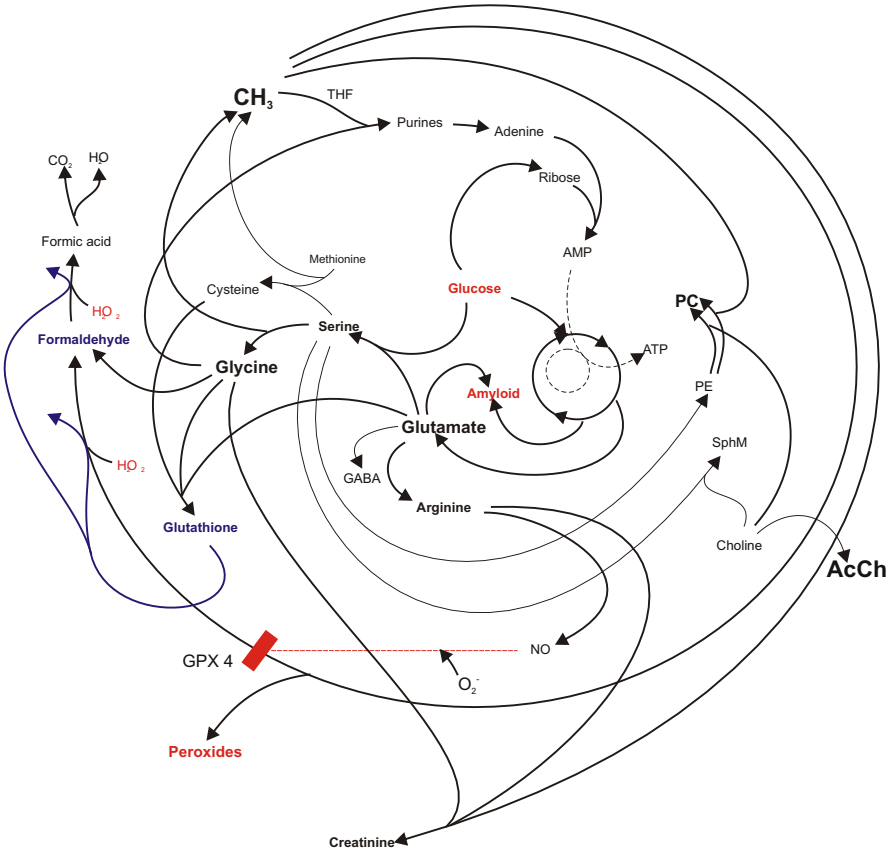
Scheme 3. Metabolic ways associated with intracellular cholesterol synthesis



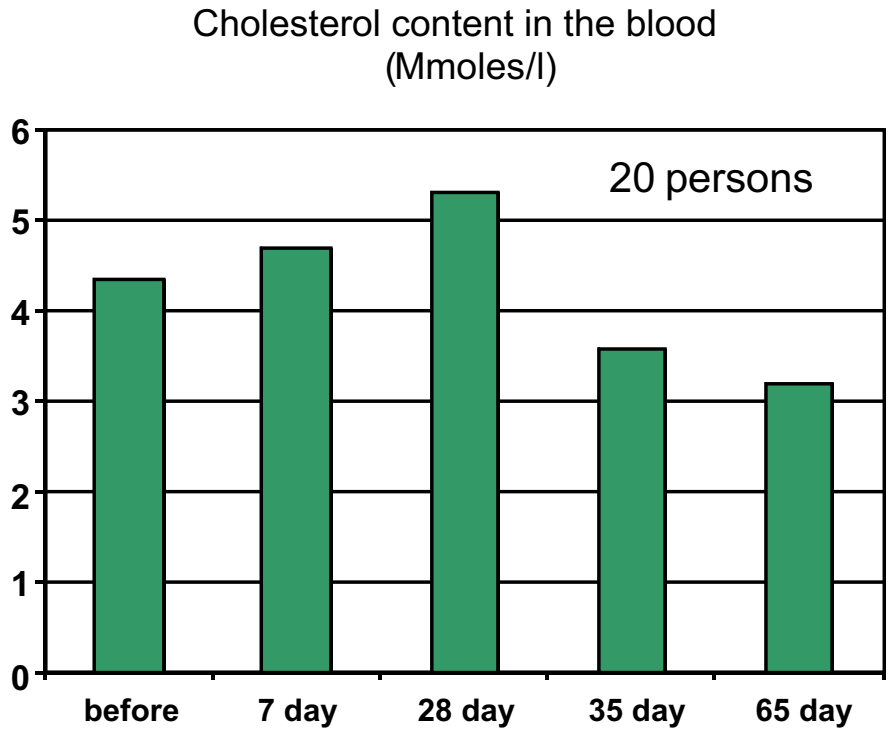
Scheme 4. Generalised scheme of human cell metabolism



Scheme 5. Glucose balance support system



Scheme 6. Alzheimer's disease pathogenesis scheme



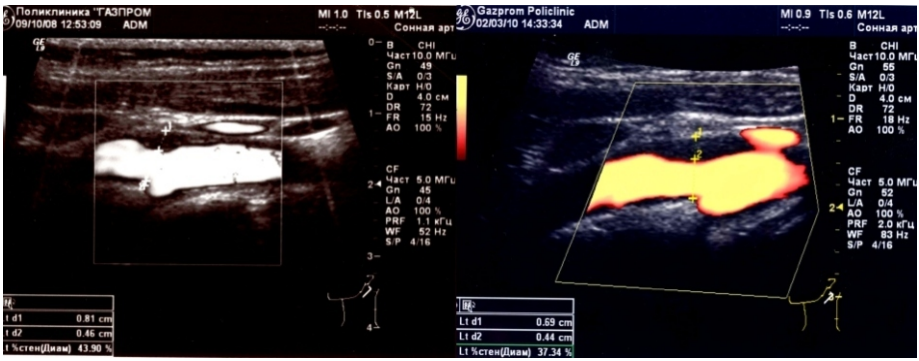


Illustration 1PNM effect

Table 1. FA action on carotid artery

		2008.10	2009.04	2010.03
common carotid artery (right side)	occlusion	30%	27%	24%
common carotid artery (left side)		43%	38%	28%
internal carotid artery (left proximal part)		48%	44%	37%
artery wall differentiation		absent	absent	**restored**
AP systolic		135-145	120	120
AP diastolic		90-100	80	80

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