VII.2. THE PROTEINS AND THE HOMEOSTASIS

The proteins are nitrogenous substances that can be found in all living organisms (animals, plants and microorganisms). ***In the absence of proteins or even when the dysproteinaemias are severe, life would not be possible.***

For our research, we are more interested in the proteins circulating in the blood and in the ones present in the structure of the cells and tissues in the human body. The source of their biosynthesis is the 20 proteinogenic amino acids. The proteins from ingested food are "fragmented" through digestion into their smallest constituents – amino acids. These cross the intestinal barrier and when they reach the "laboratories" of the cells, they are metabolized into proteins that are necessary for the functions of the human body. **Amino acids** are classified according to the importance of their contribution to the synthesis of proteins necessary to the physiologic functions of the human body, as follows:

- 8 essential amino acids (which can be synthesized only from the protein of ingested food); these are the phenylalanine, valine, threonine, tryptophan, isoleucine, methionine, leucine and lysine;
- 2 semi-essential amino acids (which can be synthesized by the human body, but not in sufficient quantities, therefore they need to be taken up into the human body from diet); they are the cysteine and tyrosine;
- 10 non-essential amino acids (which can be synthesized even without protein from food); they are: the glycine, alanine, arginine, serine, proline, glutamic acid, aspartic acid, asparagine, glutamine, and histidine.

A fact of exceptional significance to the importance of medical apitherapy *is that all amino acids – essential, semi-essential and non-essential – are found in the apitherapy products offered by Apitherapy Medical Center. As they are present in the apicultural products, their supplementation from other sources is made only where necessary and according to each clinical case.*

The synthesis of each protein in the human body is genetically determined. The union of the amino acids from the structure of each protein is controlled by a certain gene, according to information found in the structure of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The genes determine the number of amino acids from the structure of the proteins, as well as the order of their setting in the amino acid chains that they form.

According to their structure, form and solubility, the proteins metabolized in the human body are classified as:

I) ***Simple proteins (holoproteins):*** comprising only amino acids; they are:
   a) *globular holoproteins* – have spherical or ellipsoid forms: the albumin, serum globulin (α_1, α_2, β_1, β_2 şi γ), fibrinogen, calmodulin, troponin, ferritin, etc.
   b) *fibrillar holoproteins* – have elongated molecules, forming fibres which have support, protection and mechanical resistance roles: collagen, elastin, keratin, etc.; According to solubility, they can be:
      - *fibrillar soluble holoproteins* (located in the blood and muscles)
      - *fibrillar insoluble holoproteins* (scleroproteins)

II) ***Conjugated proteins (heteroproteins):*** they contain amino acids (proteins) and non-protein substances:

- *metalloproteins*: containing amino acids and metallic ions such as Fe, Zn, Mn, Cu, Co etc.[1]

- *hemoproteins*: containing amino acids and heme[2]

- *flavoproteins*: containing amino acids and bioflavonoids[3]

- *glycoproteins*: containing amino acids and carbohydrates[4]

- *lipoproteins:* containing amino acids and lipids[5]

- *phosphoproteins*: containing amino acids and phosphate residues[6]

- *nucleoproteins:* containing amino acids and nucleic acids (DNA and RNA)[7].

We do not intend to undertake a molecular biology study. We made these brief specifications regarding proteins, because we have reached a conclusion that is of great interest. In many cases, perhaps too many, people use drugs that stimulate or inhibit the actions of certain protein(s) believed to be the cause

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[1]The metalloproteins are heteroproteins which, apart from proteins, contain metallic ions (bio metals). They can have a structural role, but their primary role is of biochemical effectors. The metalloenzymes have an important role.

[2]The heme is a non-protein group forming part of the structure of haemoglobin. Each haemoglobin molecule contains four heme groups and four subunits of globin. Each heme group is made of protoporphyrin, and an atom of iron. The heme is the porphyrin-iron complex which gives the red colour to the red cells (erythrocytes, red blood cells). ***All the amino acids require for the synthesis of globin – the protein part of red blood cells – can be found in the apitherapeutic products made at Apitherapy Medical Center. The apitherapeutic products also contain substances that are necessary in the synthesis of porphyrin (glycocoll and succinic acid), the enzymes that catalyse its synthesis, as well as the iron that is found in the heme structure. All this explains well the incomparable anti-anaemic potential of the apitherapeutic products: they offer synergistically all the substances that are found in the structure of haemoglobin. It is very unlikely that any other treatment would offer such a synergy.***

[3]The bioflavonoids are ubiquitous substances from plants (they are, for example, the coloured pigments of the flowers and fruits). The flavonoids that are metabolized as flavoproteins have multiple actions: hepatoprotective, antioxidant, spasmolytic, platelet antiaggregant, vascular (protection of capillaries, venotonic, hypotensive), coronodilator, positive inotropic (favouring the movement of substances through cell ion channels), choleretic (increase secretion of bile), diuretic, etc. The therapeutic potential of flavonoids has been the subject of medical research frequently in recent years, especially during the last decade. ***It would be very difficult for anybody to find a richer source and greater diversity of flavonoids and amino acids for the biosynthesis of flavoproteins that can be found within the apitherapeutic products. Moreover, the apitherapeutic products contain flavoprotein biomolecules identical to those obtained through biosynthesis, which is highly important in the case of metabolism dysfunctions.***

[4]Glycoproteins contain proteins and carbohydrates (especially galactose and mannose). According to their structure, the glycoproteins can be mucopolysaccharides (also called glycosaminoglycans), which contain carbohydrates and mucoproteins (there are more proteins than carbohydrates). The main glycosaminoglycans are the chondroitin sulphate, keratan sulphate, dermatan sulphate and hyaluronan. When linked to proteins, the glycosaminoglycans form proteoglycans. The proteoglycans form part of the structure of the connective tissues and constitute the major components of the extracellular matrix. The proteoglycans are acidic and hydrophilic molecules (have affinity to water); they occur also in mucus, synovial fluid and vitreous humor.

[5]The lipoproteins, molecules formed through the association of proteins with lipids, are the lipids' means of transportation in the blood. Given their importance, we will return to them later in this paper.

[6]Phosphoproteins contain, along with the proteins, phosphoric acid residues (for example – casein from milk and cheese). Phosphoric acid is a mineral acid that is part of the structure of many organic substances – phosphoproteins, phospholipids, phosphocarbohydrates – and plays an important role in certain enzymatic reactions. In the form of esters (phospholipids) they participate in generating the macroergic compounds of cells, and in the form of calcium salts, they form part of the skeletal structure.

[7]Nucleoproteins are basic cellular proteins, consisting of amino acids and a nucleic acid (DNA and RNA). The chromosomes consist of nucleoproteins that contain DNA and amino acids – especially lysine and arginine – and the ribosomes contain RNA and amino acids. ***The apitherapeutic products, due to their apiarian support, represent without any doubt the most valuable source of nucleic acids for the human body, a fact which significantly increases their prophylactic and therapeutic value.***

of particular diseases. We concluded that restraining or supplementing the amino acids precursors of these proteins through apitherapy has effects that cannot be obtained by any other therapeutic means. In order to be able to do this, however, it is necessary to know the amino acid structure of the protein as well as the sources of dietary intake of those amino acids, in order to either supplement or restrict them.

The functions of protein in the human body are diverse: cellular construction, energy supply, transportation of enzymes and hormones, defence, to ensure the acid base balance, to regulate the colloid-osmotic pressure, protection and support of tissues, etc.

Proteins have a very important role in the homeostasis of the human body. We use the term ***homeostasis*** to designate the well-being or state of health, the normal physiological functioning of the human body on the whole. ***Homeostasis itself means nothing other than a stable internal environment, in spite of a variable external environment***[8]. Homeostasis is the capacity of the human body to maintain its physiological functions through continual self-regulated processes, as well as the potential to restore itself, in the absence of any medical treatment following disruptive changes.

However, the homeostasis cannot be seen as an unchangeable "gift". We would like to emphasize the fact that ***homeostasis, as a physiological state, as a normal state, is a dynamic state.*** For example, the homeostasis of the young pregnant woman has other characteristics compared to the homeostasis of a young woman who is not pregnant. Ageing, for example, can be physiological (normal) for healthy elderly people who are not diagnosed with any disease and consequently do not take any medication. However, their homeostasis, i.e the potential of their body to self regulate its functions, is declining. Over several years, our ***main aim was to identify the most accurate marker of the beginning of normal physiological aging, under the conditions of a normal decline of homeostasis***. We aimed to find both a way of delaying the beginning of the decline of homeostasis through apiprophylaxis, as well as rehabilitating the declining homeostasis through apitherapy. In both cases, the successful markers were two laboratory tests: the total proteins (TP) and SPE, which are associated in particular with the evolution of Ca^{2+}. We will use these tests as our reference throughout this paper.

We must specify that along with the proteins and in close interdependence with them, there are many other substances (lipids, carbohydrates, minerals, vitamins, flavones, etc.) participating in what we call homeostasis. As we noted above, only the holoproteins are simple proteins, while the conjugated proteins (heteroproteins) have in their structure lipids, carbohydrates, minerals etc.

When we refer to proteins, we refer to both the proteins found in the structure of human body tissues as well as those found in the ***"means of transportation"*** to and from their cells, whose purpose is to fulfil the most diverse functions. The proteins that are "made" in the cells and exude need other proteins to reach their "target cells" of the human body: carrier proteins (transporting proteins), ligand proteins (proteins that link the transported proteins to cellular receptors), receptor proteins (embedded within the target cell's membrane) that mediate the transport of the proteins through the cellular membranes. Plasma[9] is the most

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[8]Definition of homeostasis in medical literature. Although correct, we consider it incomplete. In autoimmune diseases caused by endogenic (internal) factors, ***disorder of the stable internal environment is attributed to an unstable internal environment***. Therefore, the instability of the internal environment can be based both on the instability of the external environment and on the instability of the internal one. We also include cancers among diseases that destabilise the homeostasis (immunity) of the human body. These can occur either because of autoimmunity, or because of immunosuppression, in some cases both extremes of immunity are involved.

[9]Plasma is a yellowish fluid with pH 7.4 where the blood cells are found. It represents approximately 4-5% of the body weight and contains 90% water and 10% other substances (calculated as dry residues). These are:
- *organic substances, in a quantity up to 9%,* from which 8% are plasmatic proteins, and about 1% are non-protein nitrogenous substances and non-nitrogenous organic substances (which includes lipids and glucose);

important means of transportation for circulating proteins as well as for all other substances – lipids, minerals, vitamins, etc. There are also two other means of transportation for substances circulating to and from cells in various tissues: these are the lymph[10] and the interstitial fluid[11], which irrigates the extracellular matrix[12].

- *inorganic substances, in a quantity of 1%,* represented by chlorides, phosphates, sulfates of various minerals (Ca, Mg, Na, K, Fe, Cu etc.). These minerals, generically called electrolytes, are electrically charged and become, in equal parts, anions (negatively charged ions) and cations (positively charged ions).

[10]The lymph – lymph fluid – is the fluid that circulates through lymph vessels and lymph nodes. It has a pale yellow colour, is transparent, primarily contains lymphocytes, and in a more reduced quantity, the same substances that are found in plasma.

[11]The interstitial fluid is found in the interstices (the spaces between cells of the organs). In other words, it is the tissues' extracellular fluid. The water found in the interstitial fluid hydrates the cells (their extracellular matrix). This fluid contains the substances transported by the blood and lymph capillaries into the interstices, substances that are absorbed by the cells, exudates of the cells (which are transported by these capillaries, thus entering in the blood and lymph stream).

[12]The extracellular matrix (sometimes called extracellular biological "glue") determines the physical structure and function of the tissue, and has a role of binding together and regulating the cells it comes into contact with. The extracellular matrix is made up of a network of fibrous protein macromolecules (collagen, fibronectin, vitronectin, proteoglycan, laminin, thrombospondin) embedded in a hydrating polysaccharides gel. Through the glycocalyx, a network of glycoproteins and glycolipids located on the cells' membrane, they are linked (anchored on) to the extracellular matrix. This "anchorage" insures the stability of the cells and of course, of the tissue.