A PATHOGENIC PATTERN OF THE CHRONIC RHEUMATIC INFLAMMATORY DISEASES. PATHOGENICAL LEVELS.

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SUMMAKY, We propose a new pathogenical point of view in rhumatical cornplains related to the succes we had in clinical and in preclinical tests as much as in the hospital treatment with PL and antioxidants.

The study of the rheumatic diseases shows complex processes responsible for their occurance and maintenance, presenting a multitude of tissue biochemical and humoral reactions among which only a part are recognised by all medical people. These biochemical changes are inducing some important immunological alterations.

The rheumatoid arthritis — the classical chronic inflammatory disease, is an autoimmune condition due to the antigen excess and a disease having his histocompatibility (HLA DR) with a tissular reparation present in the B lymphocites, macrophages, spermatozoa, the Langerhan's cells and the endothelial cells as well. The ankylosing spondylitis is also a chronic rheumatic inflammatory disease, in which the presence of circulating immune complexes are difficult to establish, but there is an immune participation (increase of immunoglobulines-IgG IgM) in over 60% of the patients and also by a strong histocompatibility (HLA B27). The osteoarthrosis is first of all a degenerative and age-influenced condition with no important HLA determinism and free of immune involvement.

In spite of all these the clinical aspects often presents no clear delimitated illness state. This clinical situation makes very difficult a clear diagnosis. We may find osteoarthrosis disorders with inflammatory involvement changing in rheumatoid arthritis; we may also find sacroileitis with anchilosing of the spine which began to have deformities like in rheumatoid arthritis at the fingers, and so **on.**

The pathogenic diversity of these kinds of illness have led to the normal idea of a specifical treatement for each rheumatic disease. Insted of this point of view we shall think that bellow all these differences between each illness there is a more large unity for all the rheumatical complaints. This pathogenical unification lie in the bio-chemical changes in the tissues. For that we propose different pathocenical levels insted of different rheumatical diseases, each one with his special ethiopathogenical frame. We propose the following levels: genetic, ill-organic, histo-biochemical, and cuantic.

I—the first level is the genetic one, which **is** deterministic and probabilistic.

II—the second level is the ill-organic one. It is that of the disease. Only at this level we can have an accurate diagnosis (in the sense of the classical nosological medicine).

III—the third level is the histo-biochemical, which represent the tissue (cell) biochemical changes. Such injure may be present in all diseases, but may preced its occurence.

IV—the fourth level is the quantic which shows that the biological active cells depends on the quantic molecular excitation.

The genetic level *is* represented by a polygenic system, namely the HLA system, whose genes have different sites on the chro mosomes of the VI-th pair, being clasified into three distinct groups: 1. HLA A, HLA B, HLA C; 2. the HLA D and HLA DR genes; 3. the complement components and the pro-activators of the *Ca* fraction.

The HLA D, DR and B genes inducing an intensive proliferation, particularly of the B lymphocites-cells with a protective role, are important in chronic inflammatory rheumatic diseases. All these genes produce tissue antigen of glycoproteic nature.

The whole system of tissue HLA antigens polygenically controled, a fractional unity involved in the non-self substance recognition.

The HLA system acts in close connection with plasma immunoglobulins which, in their turn, are under a rigurous ghenetic control. The antigenic HLA DR4 system, present in over 40% of the patients is important in rheumatoid arthritis. As for ankylosing spondylitis, according to some autors, the HLA B27 antigen was found in over 90% of the cases.

The ill-organic level comprises what is generally called an auto-immune aggression, an auto-immunie disease. There are changes in connective and bone tissues. Pain, tume faction, and articular stiffness with synovial proliferation, and finally with articular destruction will be clinically found.

In the rheumatoid arthritis (auto-immune disease) the following steps will be met;

the setting up of immune complexes (antigen/antibody) through an antigen excess; followed by the complement addition; the platelets injuy leading to

the releasing of vasoactive biogenic amines (kallikrein, bradyquinin, bradyquininogen etc.); the increase of vascular permeability by these vasoactive factors released by platelets and white cells; the immune complexes localization on vascular walls; the releasing of chemotaxical factors (opsonims); the tissue infiltraton by polynuclear cells and macrophages, *with* the immune complexes ingestion by iicutropbils and with lysosome enzymes realising leading to the increase in the tissue destruction rate. (proteolysis). All these pathological changes can be differentiated by laboratory tests: rheumatic factor, reactive C protein, plasma immunoglobulins etc,

The histo-biochemical level is represented by the biochemical changes at the cellular level. The cell membrane may be damaged by the poly-unsaturated fatty acids (phospholipids) peroxidation, leading to eicosanoid formation (arachidonic acid, prostaglandins, thromboxans, leucotrienes and other lipoxines). The chemical species called oxygen free radicals (OFR-s) which is ubiciiitarily because is made up and released in the cells, and is close related to the lipid peroxidation process from the cell membranes. The most important OFR-s are: the singlet, unstable, turning rapidly into superoxide a species with high toxicity and able to initiate some chain reactions;

the hydrogene peroxide, *H2O2*, a less noxious species but with the ability of forming oxidril radicals, *OH~*, the best known OFR of high toxic activity.

The tissues have a natural protection by the antioxidative system (AOS); superoxid-dis-mutase (SOD), catalase (Cat), peroxidases, cytocromoxidases, and the *macrocortin* (lipomodulin), an phospholipase inhibitor; substancess which, in physiological conditions, have the ability to protect against the toxic action of biologically active peroxides and the OFR excess as well. In pathological conditions this protection is ineffective. The excess of peroxides and intracellular OFR-s may lead to proteolysis, to cell destruction with the production of denaturated proteic substances which became auto-antigenes.

The quantic level is that of molecular electronic orbitals. There are more possible molecular electronic orbitals depending on electrons rotation and spin movements depending on the molecular energetical charge. When a molecule receives energy it becomes "exited", the electrons moving towards to upper orbitals. If very powerful, as in plasma (the forth state of the matter) the energy is increasing till the electrons may leave even the last orbital, usualy the atomic shape loosing the most part of their electrons. At the beginning the OFR-s were studied in the radiation conditions. They have a possible independent existance obtained by the breaking of the co-valent intermolecular bindings, having one or more odd electrons on the last orbital. This confers them the oxidative power which depends both on the chemical species and the quantic molecular excitation. That means that the oxidative power at the same species of OFR is dependant on the orbital bearing the electron (odd) with a higher ability to enter the redox reaction.

This quantic molecular "excitation" in the organism may depend on many other factors like: toxic substances, ingestion of oxidants, ionising radiation (exposure), microbian or viral invasion, exposing to the sunlight (a variant of ionising radiation), different kinds of traumas, some peroxidative factors such as metallic ions, exogenous oxidative ensymes etc.

INTERRELATIONS BETWEEN THE PATHOGENIC LEVELS

This frame of pathogenic levels is artificial but necessary for our intention of changig the medical thinking upon the usefulness of the nosological entitys and to propose an other approch, less analitical and more ethiopathogenical. That means we may find in the pathological reality such ill case like in our books (medical) but, we find a lot of complaits which are difficult to catch in a diagnosis.

Othewise we cope with a constant interdependence of these levels, difficult to separate. The part played by these theoretical levels for a deeper understanding of the pathogeny of the rheumatical inflammatory conditions is obvious in the manifest disease as in the pre-disease conditions (especialy), when the symptoms are expressible and strong but the laboratory findings are trivial. In the health state, the genetic, ill-organic, histo-biochemical and quantic levels may be imaginate in a normal, functional balance.

What the probabilistic determination of the genetic level might mean? An organism, a body, with a certain histocompatibility antigen can, may, permit only "certain group of disease", all the others being forbiden to it. This determinism is not strictly compulsory, as in genetic imperfections, but probabilistic. Not all HLA B-27 and HLA DR-4 bearing humans develop ankylosing spondylitis, psoriatic arthritis, Reiter disease, or rheumatoid arthritis. Only a few will develop one of these diseases and solely in some favorizing conditions, either internal (a poor or strong expressed immune system) or external (microbian or viral infections, different traumas, chemical or physical factors).

The genetic level will also influence upon the ill-organic or quantic levels through the anatomo-functional pathways. The antioxidative system enzymes are unlikely codified whithin the various organs. Their anti-oxidative action may also be different. The quantic level is, in fact, the quantic expression of cell redox reactions. In other words, we

should understand the one single chemical reaction has various manners to **be achived: tune of** reaction, underlayer parameters, beeng dependent to the quantic molecular excitation status of reactants.

In quantic and ill-organic levels, their disturbance leading to inflammation (occurence) are disease precursors. Various inflammatory-type sufferings difficult to enter **in** a nosological frame; a nosological place (sub-clinical evolution or tendency towards spontaneous remissions) may be present some years or month before the setting-up .of a chronic rheumatic inflammatory disease. A possible efficient prevention of a chronic rheumatic inflammatory disease should take this aspect in account.

In case of important organic disorders (articular destruction and subsequent ankylosing), the diagnosis is more easy but the therapeutic is ineffective and expensive.

How the genetic level can be influenced by the other levels taken as a whole? In chronic rheumatic inflammatory diseases,-the anti-oxidative system becoming nonreactive, an accumulation of intracellular peroxides and OFR was found. This leads to the aggressioning of the lysosomal ARN, the transfer ARN, and directly of nucleous ARN. Consequences? The disturbance of the proteic synthesis, and an antigen excess through proteolysis and cell destruction. The increas ing of the auto-agresion is ready.

THE INTEGRATION THEORY OF THE PATHOGENIC AND RESTORING CIRCLES

On the ocassion of the histo-biochemical levels description we spoke about disturbances by biological peroxides and oxigen radicals accumulation. The eicosanoids accu mulation by oxidative degradation of phospholipids from cell membranes may represent the first pathogenic circle with positive feed back (the inflammation "has a growing-up in pathologic conditions). The second pathogenic circle with positive feed back is represented by intracellular oxigen radical growing-up in pathologic conditions as well. Circles with negative feed back, oposing to the oxidative disturbances are also present in response to those with positive feed back. We'll consider these negative feed back circles as having a restoring action.

The first restoring circle, corresponding to the first pathogenic circle, at cellular level is due to the action of macrocortin (lipo-mpdulin, the inhibitory protein), as polypeptide with a molecular weight of 44,000 daltons. Macrocortin is a tissue hormone produced and stored in macrophages, being considered as a secondary messenger. Its action is to limit the phospholipase, which leads to the reduction of the arachidonic acid, prostaglandin, leucotrienes, thromboxan, and other lipoxins production, therefore to the reduction of the biologically active peroxides in inflammation.

The second restoring circle, corresponding to the second pathogenic circle, of the AOS system, made up, in its turn, of anti-oxidative enzymes, glycoproteins (transferrine, ceruloplasmine, lactoferine), histones, haptoglobins, albumins, glucose, ascorbate, tocopherol, cystein, methionin (aminoacids), uric acid, ureea, metallic ions (zinc, selenium) etc. All these substances reduce the aggressiveness by OFR-s.

An autoimmune aggresion by antigen excess is realized in the case of chronic rheumatic inflammatory disease. We have seen that this antigen excess is due to an increase in eicosanoids and intracellular OFR quantity. The immunologic aggresion is realised by this biochemical pathway (proteolysis and cell distruction). The physiologically active restoring circles became non-effective in this situation. The pathogenic circles are self-growing and they lead to the rheumatic chronic complaints, as well, by producing and maintaining the inflammatory symptomatology.

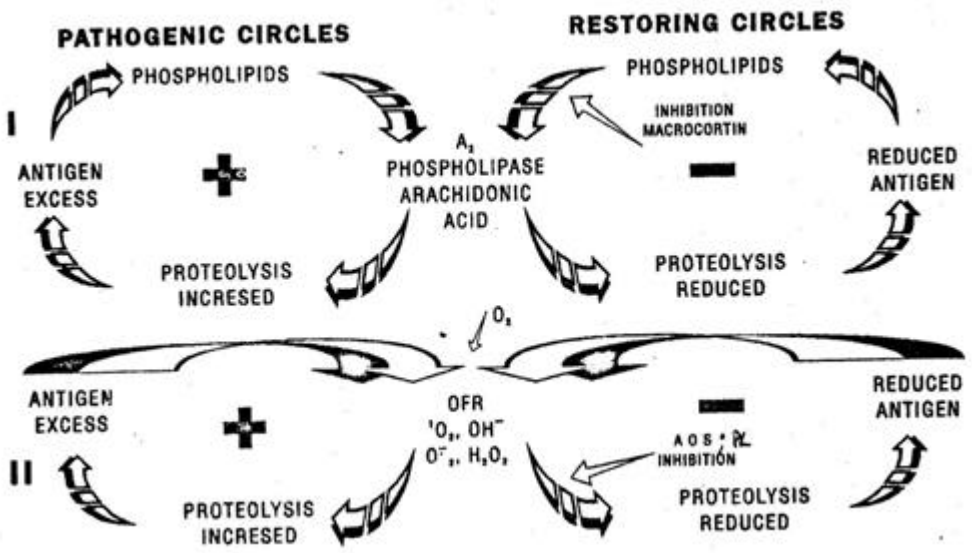
Therapeutic consequences*:* All this four levels of pathogenicity are closely related and it is not necessary to give separate treatements for each level. If we can act with success on one level, all the other will be changed in to health, the physiological function will be restored. By this way we can influence positively the disease in his evolution or even in his occurence.

The choise of the treatment? The efficient one, without side effects, or the little possible, without damage, without the risk of inducing a yatrogenic much worse illness than the natural one. For that I propose to each physician to be conscient that he may help not to injure. I know it is difficult such a choise, but that is why we spoke about good physicians. The possibility of a genetic treatment is not yet actual, and we kan't **know** how he will be.

The ill-organic level tretment is trivial for the physician and leed to different treatments for different illnesses. The difficulty began when we haven't a clear diagnosis, when the evolution of the ill state is not easy to be put up in a frame. Sure, we can expect and to offer the time of the ill state to express an illness, that means a knowing ill state. What "we don't know it is only a transitory ill state. An other approch is to begin the treatment immediatly and trying to avoid, or to prevent, the illness or the person. Such a preventive therapeutical medicine may take in atention the histo-biochemical and the quantic changes which produce, by the way, inflammatory symptoms (rubor, tumor, color, dolor, and functional defin-cicncy). Such a treatment will reduce the molecular excitation directly, if it is possible, or indirectly by stimulating the macro-cortin activation in macrophages (the first restoring circle) administrating injectable polipeptide.s (PL), and antioxidants (Orgotein, methionin, glutathion, ascorbate, tocopherol, alopurinol, selenium a.s.o.), able to support the anti-oxidative restoring circle. For the time being we would like to focus upon such a treatment, which could be considered as specific to the biochemical and quantic levels, yet unspecific from the ill-organic point of view. The preventive treatment of the various forms of rheumatic diseases means to avoid the evolution of the illness, or even to preserve the body against a clear ill state by treating the first inflammatory symptoms.

Instead of conclusions: The main benefit of this paper will be if I succed to change, to enlarge, our point of view, in medical practice. We must keep in our mind that the nosological entitys are helpfull, but artificial and restrictive. If we don't find what we hope to find we give only slight symptomatical medicines and we prefere to give time to the illness to agravate.

Using this pattern we shall succed to stop the illness by treating his early stages of evolution physiopathologicaly. By this way we may keep the ill person in early inactive stages of illness, or to avoid the later distructive stages, especialy in the rheurmatical complaints.



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