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INFLAMMATION AND PHYSIOLOGICAL REGULATING MEDICINE

– NEW IDEAS AND INNOVATIVE MEDICAL PRODUCTS

SUMMARY

Cytokines (CKs) are proteins secreted by cells of both the innate Immune System (true mobile Nervous System) and the acquired Immune System in response to antigens that induce various responses according to the cell types involved in the mechanisms of stress-immunity-inflammation.

Due to their peculiarities as biological motors-messengers-modifiers-modulators - oriented toward coherent (homeostatic-homeodynamic) equilibrium - and consequently to preservation of the individual - CKs appear in the early stages of the history of life: the Epstein-Barr virus contains a homologous gene to IL-10; the transduction mechanism of IL-1 is Toll type, from the name of the same transduction mechanism discovered in Drosophila. The evolution of the species is nothing more than the evolution of the Immune System. CKs have a direct general mechanism of action on activation (differentiation + lymphocyte growth) and implementation (elimination of the stressor). CKs secretion is: 1) a brief and self-limiting event; 2) pleiotropic, redundant, synergic, antagonist. CKs influence the synthesis and action of other CKs (immune cascade confirmed by natural selection as the hormonal, coagulation, and nervous cascade) requiring specific target receptors boosted by external signals to the target cells, which react by modifying gene expression (start-up of silent genes).

- A complete and effective targeted biological response is achieved with the occupation of a minimal quantity of receptors (e.g. no more than 1% - 2% for IL-1) and with characteristically low-dose and low titred physiological dilutions all below Avogadro's Number. Molecular intelligence, coherence domains and electromagnetic superdomains are topics verified and accepted by the international scientific community. Together with the physiological dilutions (the same that operate in living organisms) they are administered with dedicated and innovative medical products characteristic of Physiological Regulating Medicine. They represent a major advance in homeopathy and homotoxicology, by endorsing them as an advanced objective in progress workshops for future developments of *low-dose* sciences.
- Immune Physiological Regulating Medicine - resetting, promotion and coordination of the altered immune language - includes the use of PRM complex remedies.
In particular, the characteristics of Guna®-Arthro drops, Guna®-Flam drops and Guna injectable ampoules for pain therapy are highlighted.

KEY WORDS

INFLAMMATION, CYTOKINES, HOMEOPATHISED CYTOKINES, PHYSIOLOGICAL REGULATING MEDICINE

INTRODUCTION

Inflammation is useful to the body as it is aimed at the limitation, destruction and elimination of etiologic agents or cellular detritus produced following tissue damage. The final effect is the restoration of the pre-existing state prior to the stressor with repair of the damage. Peripheral memory traces of the event remain at the dendritic level, at the central level and in the macrophages in the form of an *electromagnetic template*.

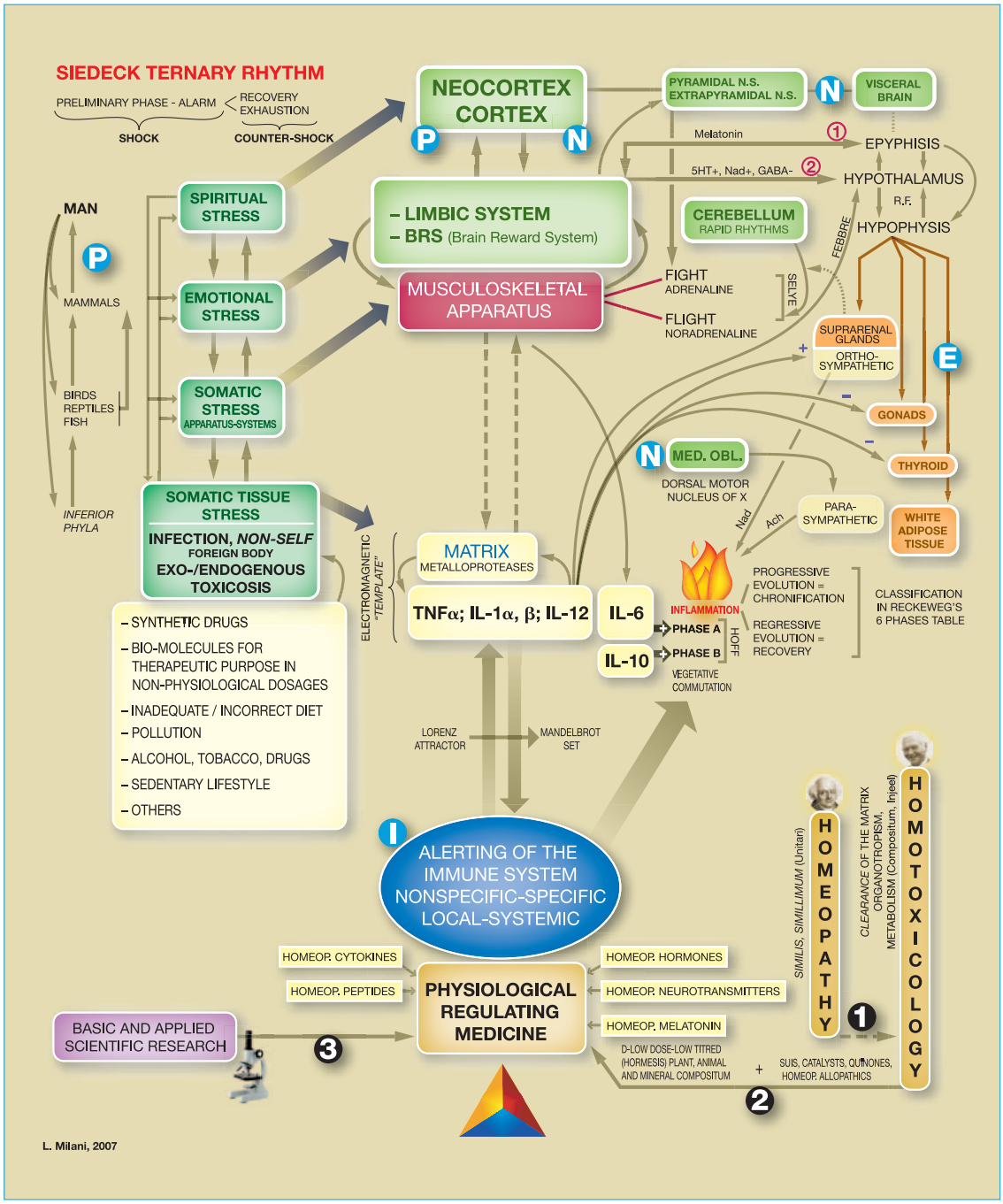
- Inflammation is an essential defensive phenomenon whose development and conditions are articulated by molecular events programmed according to an **encoded procedure** through mechanisms of convergent evolution: 1) the Epstein-Barr virus contains a homologous gene to that of human IL-10 that encodes a product with similar activity to that of the natural cytokine. This makes it possible to see that the acquisition by the virus of the IL-10 gene during evolution has conferred on the virus the capacity to inhibit the immune response of the host and, consequently, a selective benefit for its own survival; 2) the IL-1 transduction mechanism is *Toll type*, named after the one found in *Drosophila melanogaster*, the fruit fly; 3) IL-1 α and IL-1 ß share the same ribbon-like structure folded at 12 points like the growth bonds of heparin and the Kunitz-type inhibitors of trypsin; 4) receptor similarity of a number of chemokines with the Duffy AG that mediates the penetration of *Plasmodium vivax* into erythrocytes. These examples of "molecular archaeology" demonstrate how the phylogenetic *continuum* is accomplished through progressive, imperceptible transformations of the archaic genomes, but only for the essential functions - among them molecular defense and protection - the base-model (pattern) has remained essentially unchanged in comparison to the one that was active millions of years ago. This type of "immune reductionism" nevertheless had to be put to the test, not only by external transformations, but also in man by transformations induced by his "reading" of the world, by the interpretation of phenomena, logical and analogical abilities, the awareness of intellectual superiority in comparison to other animal creatures, the sensation of being different and conscious, the unconscious feeling of carrying an efficient and effective frontal neocortex.
- **Tissue** stress (infection, nonself, exo-/endogenous toxicosis) of the inferior Phyla turns into **somatic** stress involving complex apparatuses and systems in

fish, reptiles and birds leaving the field open to the **emotional** stress specific to mammals that turns into a typical **psychic** and **spiritual** stress - real because it is at the highest point of the evolutionary pyramid - in man.
The alerting of the non-specific and specific, local and systemic Immune System (I.S.) through neuro-endocrine mediation creates the basis for the survival of the individual and the species, the *condicio sine qua non* for shaping - by adapting it -the appropriate individual response to internal and external requirements (TAB. 1). The relationships between the human Nervous System and I.S. are numerous (Milani, 2006):

- Structural polyphormism
- Immaturity at birth
- Short- and long-term memory
- Amplification mechanisms of the afferent stimuli
- Control of the stressors in excess
- Auto-inhibition
- Local and remote effects
- Various stereotyped responses.

The I.S. can be interpreted as a true *mobile* Nervous System.
The junction where stress, immunity and pain are sorted is represented by the limbic brain which influences reactive behaviour with the memory-affective-emotional dimension (TAB. 2).

➤ Thus, the same, with an almost identical genome; but different, therefore, due to the individuality of the cultural and emotional experience.
Purposes that are, so to speak, "historical", "phyletic", almost mechanically

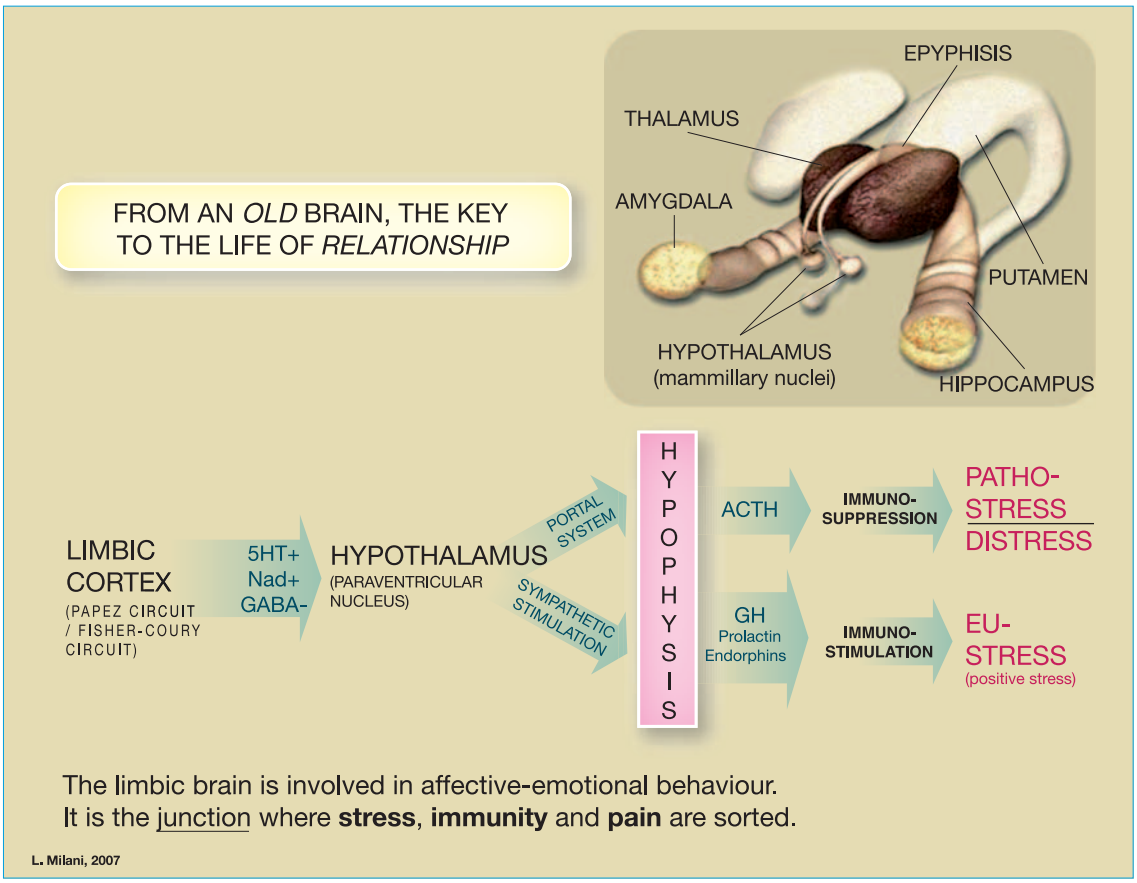


TAB. 1

Synoptic table illustrating the different bonds, correlations and influences that the single elements of the P.N.E.I develop in response to a stressor in the genesis of inflammation. Below: role of Physiological Regulating Medicine that unifies selected concepts from Homeopathy, Homotoxicology and basic and applied scientific research, promoting an innovative, preventive and therapeutic method, responding to the needs of modern biological medicine.

TAB. 2

A stressor of similar intensity and duration produces different (sometimes opposing) effects in individuals differing by the peculiarity of the biological unicum expressed by each person. To this is added a common basic stereotyped response not depending on individual need but on the behaviour of the species.



predetermined emerge in the N.E.I. responses of every individual into a common file; but it is really the P. the acronym header that informs the subsequent N.E.I cascade by making each one - in the biological sense - unique and unrepeatable. This difference is greatly valued by Physiological Regulating Medicine: a standardized medical therapy must always be integrated from individualized therapeutic approaches, which are varying, dynamic and dedicated in accordance with the evolution of the clinical condition. In such a context, the concept of homeopathic *similimum* fits perfectly with this statement, demonstrating its puzzling modernity.

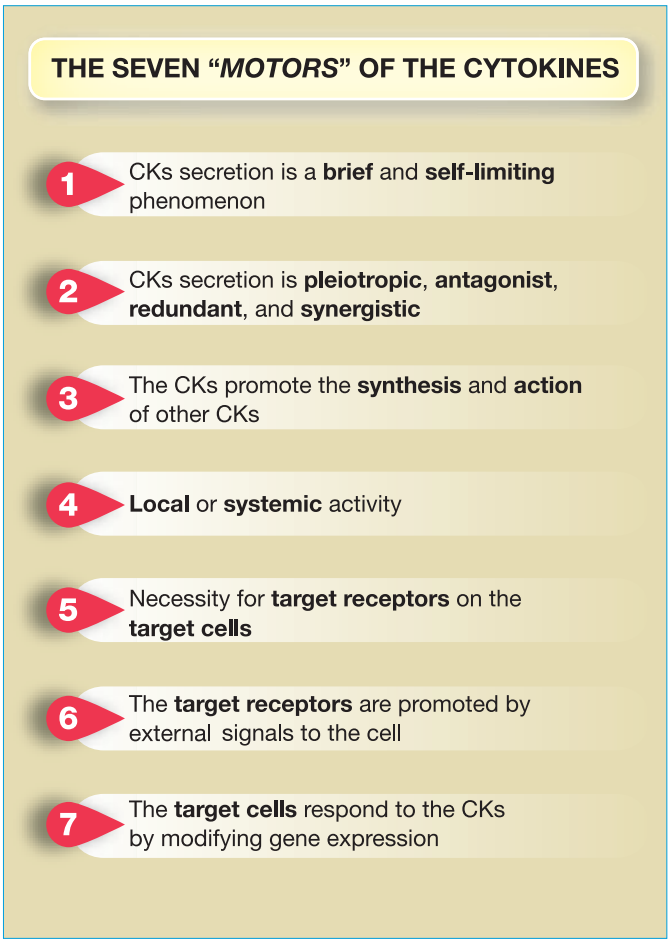
CYTOKINES AND INFLAMMATION

Cytokines (CKs) are peptides produced by different lines of cells of both the innate and specific I.S. in response to a wide variety of inducing stimuli, mainly germs and antigens that produce various responses depending on the cell types involved in inflammation and immunity. In some ways, they are similar to the peptide hormones though these are secreted by specific endocrine structures: they partially share the characteristic of highly informative molecules on target cells and tissues due to their *telecrine* function, acting on targets at a site different to the one in which they were produced (the CKs *autocrine* action on the cell that has secreted it and *paracrine* action on various neighbouring cells are specific to the CKs). This is a *para-endocrine* function as it is transported by the blood in order to interact with the cells that have the receptors they can bind with.

The functional characteristics of the CKs are illustrated schematically, but in essence, in TAB. 3. The second function combines 4 effects: **pleiotropism**, the capacity to affect more target cells, as in the case of IL-4 (the response to the stimulation varies according to the cytotype with which they have reacted through specific high-affinity receptors expressed on the surface of the target cells); **antagonism** as with IFN γ activating and IL-4 inhibiting macrophage function; **redundancy** as with IL-2, IL-4, IL-5 which induce the proliferation of B lymphocytes; **synergy** as with IFN γ and TNF α by activating the major histocompatibility complex (MHC) on many cell types. An effect not sufficiently exploited is the **synergy of action of the CKs** (explosion of effects) in sequence (cascade of CKs). One hour after the inoculation of LPS (endotoxin from Gram- bacteria) a peak TNF α concentration is obtained experimentally. While the TNF α activity is becoming exhausted, the activity of IL-1 is boosted; as this declines, the activity of IL-12 increases. The three CKs are secreted only by macrophages and NK cells. The whole proinflammatory phenomenon lasts 6 hours on average, ensuring that a suitable status is maintained. The organic response is thereby optimized by a steady, secure and effective *plateau* so that the host can ade-

TAB. 3

The "motors" of the CKs.



quately neutralize the cytolytic effect of the LPS. Individually, none of the three CKs is able to neutralize the LPS, even in greater than physiological concentrations. On the contrary, they trigger receptor down-regulation with inhibition of the specific goals.

Physiologically, CKs are not stored in the cells; their synthesis requires the transcription of genes that have been silent until now and are activated after stimulation of the cell. Such transcription activation is transitory. The RNAm that encode the CKs are unstable. Consequently, the secretion of cytokines is brief and self-limiting so the intervention of more CKs "in relay" is necessary to support a biologically targeted effect (telenomy of the natural phenomena).

These 4 effects are responsible for the **Siedeck ternary rhythm**: after a first phase of activation in which lymphocyte differentiation and growth occur (Phase A of Hoff's vegetative commutation - proinflammation = Selye's shock phase) follows the implementation phase through the attempt to eliminate the stressor (anti-inflammatory Phase B of Hoff's vegetative commutation = Selye's counter-shock phase). Acute inflammation includes three major phenomena: 1) vascular alterations - neurogenic inflammation (initial vasoconstriction, active hyperemia, passive hyperemia and stasis) which involve the caliber and blood flow in arterioles, venules and capillaries; 2) formation of exudate; 3) migration of leucocytes in the extracellular matrix (ECM). The vasoconstriction induced by adrenaline and the subsequent vasodilatation in which histamine, serotonin and prostaglandins E2 and G2 are involved, are equivalent to Selye's fight phase. The allopathic use of antihistamines and COX-2 inhibitors (cyclooxygenase - lipoxygenase) inhibits the vasodilatation by stopping passive hyperemia, diapedesis, formation of exudate and phagocytosis, with a resulting stand-by state and toxicosis of the ECM due to the accumulation of antigen detritus. The prolonged use of these drugs may result in chronic and autoimmune pathologies. The angioinflammation turns into histoinflammation.

- The Biological Division in the Reckeweg Six Phases Table is nothing more than the watershed between angio- and histoinflammation. The sudden interruption of the phenomena following on Phase A can indicate temporary abolition of the symptoms, resetting the physiological course that is articulated by a strict and predetermined timetable: a tissue that is not completely healed (end of Phase B) represents - even after years - a tissue of less resistance, serious irritation for the CNS, a prodrome for various diseases, even involving organs derived from different embryonic germ layers from those from which the organ originates that is the site of the earlier pathology. In actual fact, the recovery process is achieved **when a balance is established between Th1 and Th2** immunity regulated by Th3 immunity, immune tolerance - memory that fights the plus-inflammation and that becomes established as a result of a functional deficit of the Th3 system.
- Terms such as "relapse", "slow and difficult recovery", "chronification", "progressive vicariation" are different expressions highlighting a single concept: non-physiological recovery.

No therapy is really effective if it does not respect the *clock* that million of years have standardized.

KEY-LOCK - STEREOSCOPIC COMPLEMENTARITY

CKs receptors are transmembrane protein structures with an external part and an internal part that triggers the cascade of signals (transduction).

Two molecules are attracted only if they resonate at the **same frequency of oscillation**. CKs receptors are divisible into 5 families in accordance with their three-dimensional morphology; each of them induces a different mode of transduc-

tion (TAB. 4). Several receptors are coupled to others control the amount of information: an interesting analogy is with the inhibitory corticospinal nervous tract blocking an excess of peripheral information, a type of protective relay that interrupts the circuit so as not to damage the apparatus.

A paradigmatic example is provided by IL-1 R2 (IL-1 Ra, IL-1 ra), present only on the B lymphocytes, which does not translate **any** activation signal; it is a real molecular trap, a decoy or false receptor that blocks the excess IL-1 in order to limit and circumscribe the inflammation and prevent the B lymphocyte from immediately producing IgGs, thus allowing the inflammation to become activated. This inhibitory receptor, which is competitive-antagonist of the real IL-1 receptor (IL-1R1) seems to have evolved before the division of IL-1 into the two subclasses IL-1 α and IL-1 β.

- *Anakinra*, a recombinant IL-R2, *etanercept* and *infliximab* which block the TNF α receptors have recently been introduced in the conventional therapy of rheumatoid arthritis.

These drugs have opened up interesting therapeutic perspectives although the negative side effects are particularly impressive. For *anakinra*: pain, bruises, bleeding at the injection site, which frequently force the patients to discontinue treatment (Cohen, 2002).

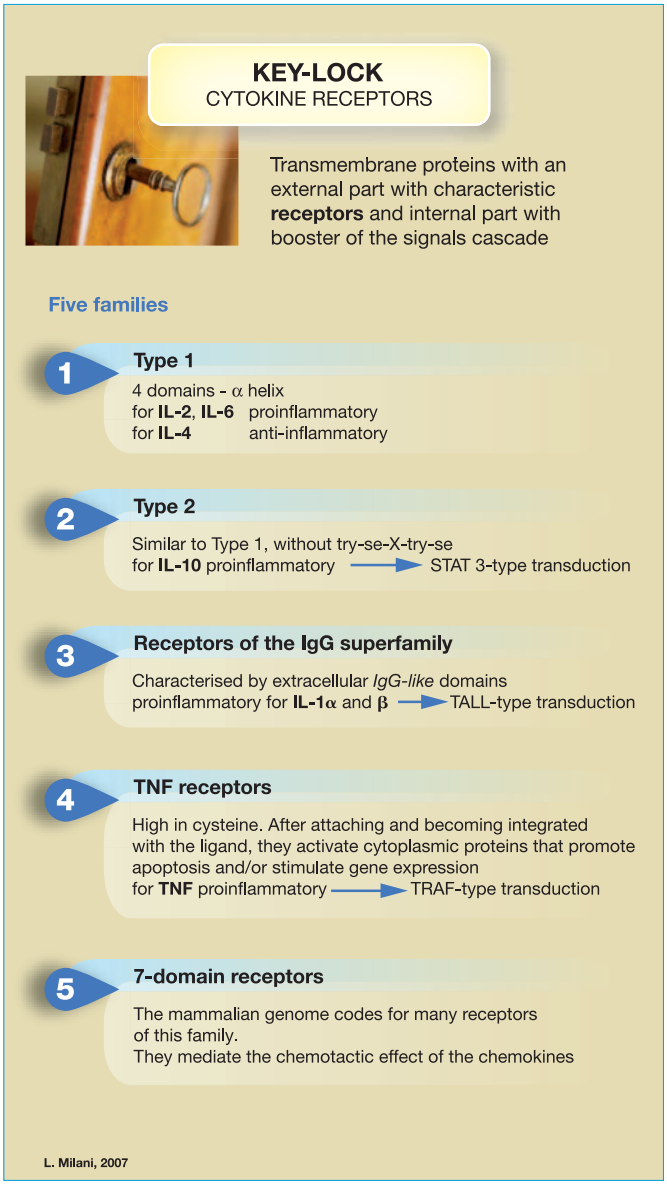
Other adverse reactions are headache and abdominal pain (Cohen, 2002). For *etanercept* and *infliximab*: neutropenia, increased incidence of serious infections.

The receptors bind the CKs with high affinity and a constant dissociation of **10^{-10}-10^{-12}** M.

Consequently, to make a receptor perform its function, **very low cytokine concentrations are sufficient** because the number of receptors per cell is relatively low (≈ from 100 to 1000). Besides the intrinsic characteristics, the concentrations of CKs are very important for therapeutic purposes as different concentrations induce different effects.

For example, low plasma concentrations of TNF and IL-1 (10^{-9} M) induce: 1) leucocyte activation, 2) secretion of IL-1, chemokines and adhesion molecules [local proinflammatory effects]; in moderate concentration: 1) fever (hypothalamic centre for temperature regulation); 2) acute-phase proteins (liver); 3) production of leucocytes (bone marrow); at plasma concentrations (≥ 10^{-7} M): septic shock with hypoglycaemia, low endothelial resistance and formation of thrombosis, low cardiac output. The similarities between the actions of TNF and IL-1 depend on the common transduction of the signal using similar proteins, though they are structurally different. The effect of the different concentrations of a biological active principle had already been experimentally highlighted (Pennec and Aubin, 1984): 10^{-5} M aconitine causes heart fibrillation; 10^{-7} M bradycardia; 10^{-18} M has no effect on a healthy heart and there is a normalization of the rhythm in the preintoxicated, isolated and infused eel heart (*Anguilla anguilla* Linn.). In a recent micro-auto radiographic receptor study (Stumpf, 2005) it was shown that low-dose and low-titred substances interact with the cell nucleus, while higher concentrations trigger a cellular response at cytoplasmic level.

Chronologically, the effects of low-dose immuno-modulants have been reported by Poitevin *et al.* (1983), Wagner *et al.* (1986), Poitevin *et al.* (1986), Wagner *et*

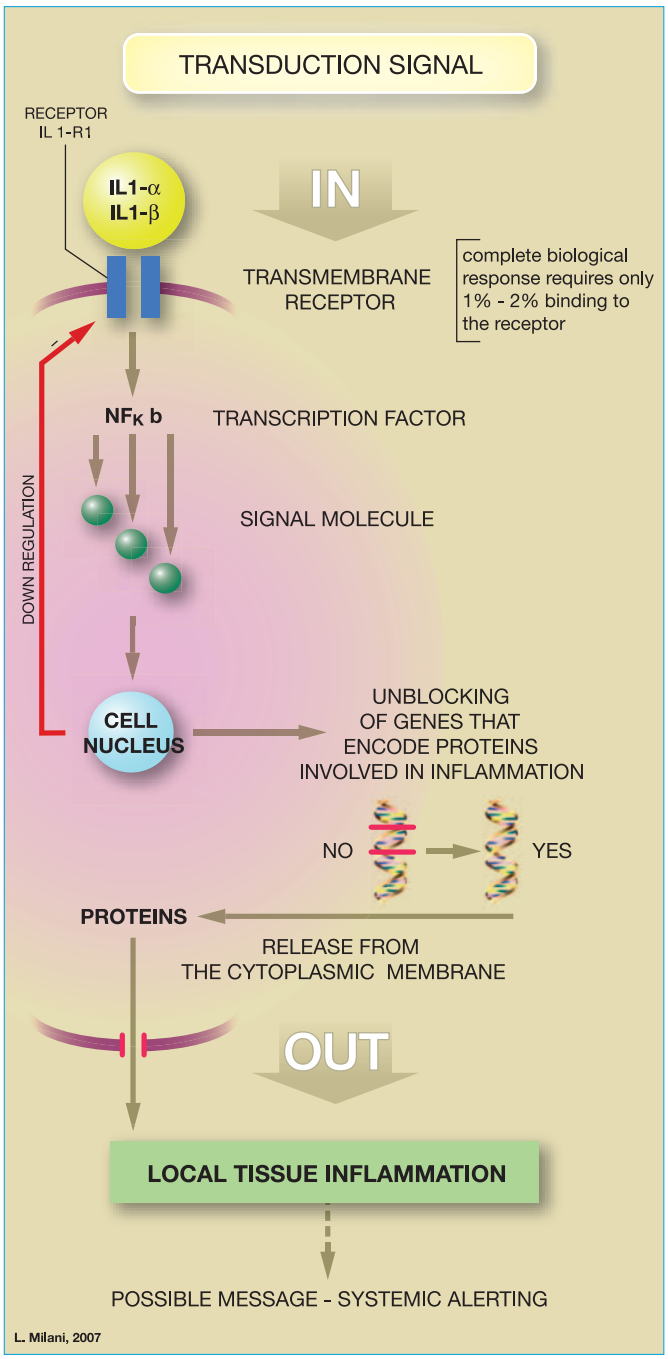


TAB. 4

The five family types of CKs receptors. Some salient characteristics of the receptor of the CKs are shown.

TAB. 5

Synoptic table illustrating how IL-1α and β bind to the IL-1 R1 receptor. -This is the prime mover of the coding of proteins and inflammatory peptides.



al. (1988), Davenas *et al.* (1988), Poitevin *et al.* (1988), Daurat (1988), Enbergs and Arndt (1993), Enbergs (1998), Belon *et al.* (2004), Jäggi *et al.* (2005), Amadori *et al.* (2007).

- There is no receptor turnover since the receptor synthesis is regulated by appropriate external signals to the cell: the ligand CK and the specific receptor are neosynthesised only if required and simply do not exist when they are not needed, complying closely with the natural principle of parsimony.

CONTROL OF INFLAMMATION - FROM PHYSIOLOGY TO THERAPY -HOMEOPATHISED CYTOKINES

The control and the specific sequence of the activator or suppressor stages of the immune response are mediated by cells through the release of proinflammatory and anti-inflammatory CKs:

- **Th1** or proinflammatory: TNF α, IL-1 α, IL-1 β, IL-2, IL-6, etc. (accepted today: 13),
- **Th2** or anti-inflammatory: IL-4, IL-10, etc. (accepted today: 4).

The classic proinflammatory CK and the first to be discovered is IL-1 (α and β variants). Once bound to the membrane receptor - the α barrel (12-stranded beta-sheet structure) so-called from the distinctive form of overlapped circles spaced out by linear structures, a receptor shared with the M-CSF-Mononuclear phagocyte colony stimulating factor, of the cells of the endothelium, epithelial keratinocytes, platelets, neutrophils and microglia, it enters the cytoplasm and binds to the NF-$_k$b transcription factor: this complex stimulates several signal molecules which can release several silent genes at nuclear level allowing them to encode proinflammatory proteins operating at the level of the surrounding tissues.

The message also reaches the CNS by inducing fever (endogenous pyrogen) and alerting of the system (TAB. 5).

All the main functions of IL-1 α and β are illustrated synoptically in TAB. 6.

- On the whole, IL-1 (α; β) activates type 2 cyclooxygenase (COX2) (effect **1**), prostaglandin E2 (effect **2**), nitric oxide (effect **3**), activating and accelerating the inflammatory process.

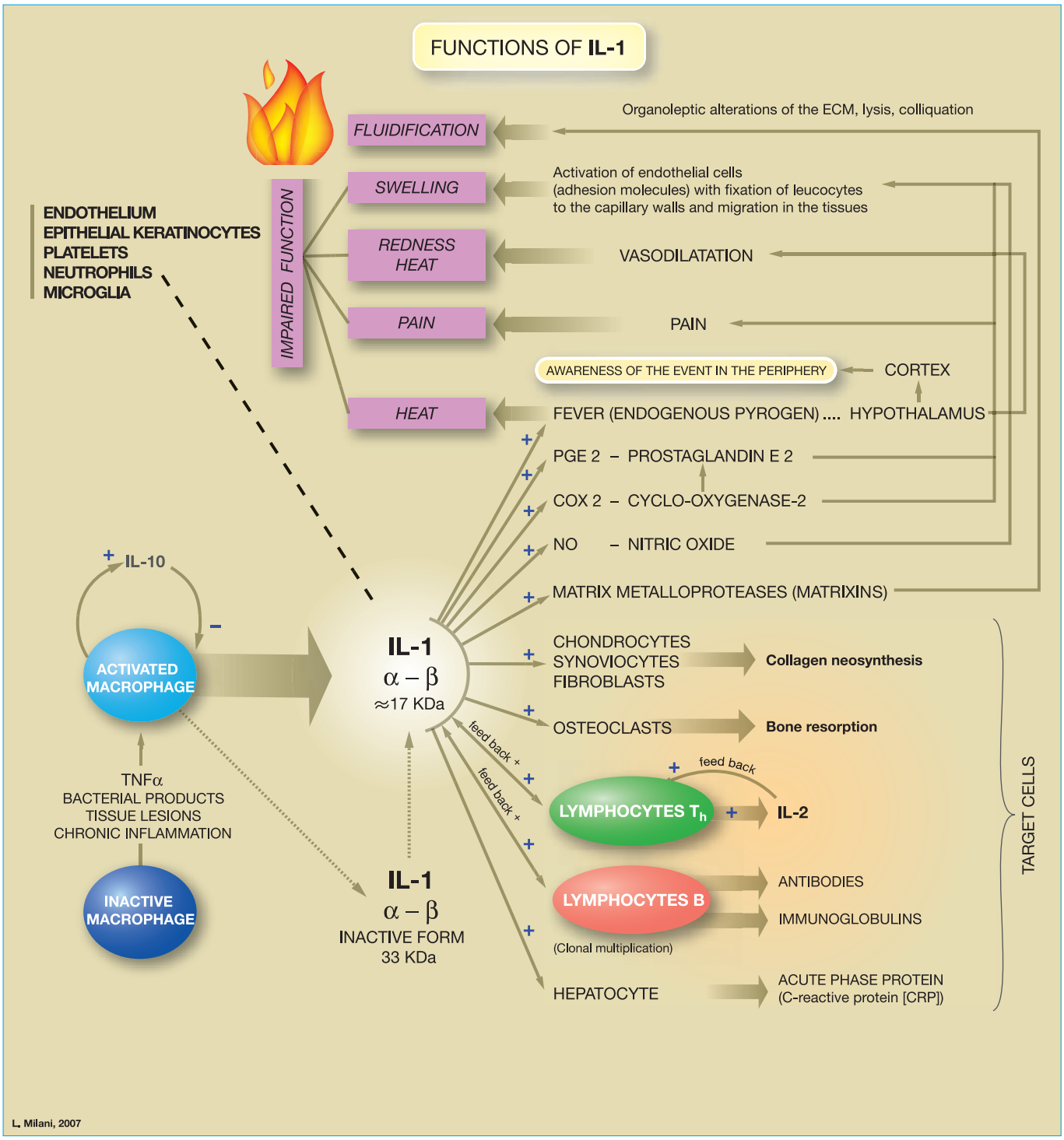
➤ Consequently, the Anti IL-1 (Anti IL-1 α, Anti IL-1 β) inhibits effect **1** (like the NSAIDs), effect **2** (like the corticosteroids) and effect **3** (like the salicylates), without the negative side effects induced by these synthetic drugs.

The homeopathised Anti IL-1 α and β are therefore used successfully in the therapy of the osteo-arthro-myofascial pain (inflammation of joints and myofascial structures) as according to the concepts specific to Physiological Regulating Medicine (PRM).

PRM IN INFLAMMATION AND PAIN CONTROL

Patients suffering from painful and inflammatory diseases of orthopaedic, rheumatologic and traumatologic nature account for 25-35% of all patients consulting a general practitioner.

A great resource for a general practitioner is to be able to use effective medical products acting rapidly and with no negative



TAB. 6 **Activity, phenomena, epiphenomena and proinflammatory effects of IL-1α and β.**

nor recurrent side effects. PRM is based on a wide range of medical products having all the above characteristics besides being innovative in some respects.

▶ GUNA®-ARTHRO drops

GUNA®-ARTHRO is a PRM product composed of 5 therapeutical *cores*: Anti-inflammatory, Antidegenerative, Metabolic, Trophic and PNEI *core*.

- Uses: Osteoarticular degenerative process of small joints (e.g.: in combination with Guna®-Polyarthritis + Guna®-HandFoot) and large joints (e.g.: in coxarthrosis or gonarthrosis in combination with Guna®-Hip + Guna®-Muscle), inflammatory disease of the joints (in association with Guna®-Flam), osteoporosis (in association with Osteobios®).

▶ GUNA®-FLAM drops

GUNA®-FLAM is a PRM product composed of 4 therapeutic *cores*: Antiseptic, Antalgic, Neuro-endocrine and Anti-inflammatory *core*.

The Anti-inflammatory *core* includes 1 nosode (*Pyrogenium*), 4 single reme-

dies of plant origin (*Aconitum, Belladonna, Bryonia, Phytolacca*), 3 single remedies of mineral origin (*Ferrum phosph., Hepar sulph. calc., Copper gluconate*), 2 metabolites of Krebs cycle (*Natrium pyr., Citricum ac.*), 1 single remedy of animal origin (*Apis*) and 4 specific PRM remedies (Anti IL-1α 4C, TGF 1β 4C, IL-10 4C, Melatonin 4C).
- Uses: acute and chronic inflammations, pain of inflammatory origin.

▶ GUNA INJECTABLE AMPOULES FOR PAIN THERAPY

The 10 Guna injectable ampoules for Pain Management are specific and selective for osteo-arthro-myofascial pain and pathologies of every single somatic anatomic part: Guna®-Neck, Guna®-Thoracic, Guna®-Lumbar, Guna®-Shoulder (shoulder and elbow), Guna®-Hip (hip and knee), Guna®-HandFoot, Guna®-Ischial, Guna®-Polyarthritis, Guna®-Muscle and Guna®-Neural.
Nine out of 10 contain Beta Endorphin 4C; 8 out of 10 contain Anti IL-1α 4C and Anti IL-1β 4C, having a great pain-killing and anti-inflammatory effect.
The homeopathic *physiological* microdoses involve no negative side-effects, and help avoid any trouble concerning tolerance as well as pharmacological catabolite overload in ECM and organs.

▶ Guna®-Arthro, Guna®-Flam and the 10 Guna injectable ampoules for Pain Management may be used in combination in an outpatient or home treatment according to the needs of every single clinical case.

CONCLUSIONS

For more than 150 years, due to the intrinsic characteristic of symptomatic medicine, even with the integration of new pathogenesis, classic Homeopathy has remained closely and structurally anchored to its historical roots (Milani, 2007).
Medicine of symptoms, if not adequately integrated with the new advancement of the *low dose - low titred* homeopathic immunobiotherapy, is destined to disappear: it does not have a chance of progressing.

By means of an ambitious project, Physiological Regulating Medicine (PRM) has fully achieved the theoretical proposals of Prof. H. Wagner.

In the 3rd Italian National Congress of Homeopathy: "Physics, biology, medicine. A unifying approach" organized by A.I.O.T (Italian Medical Association of Homotoxicology) in 1988, he pointed out (*I quote*) the "characteristics of the immunotherapies to achieve the strengthening of the non-specific defenses" which must have:
1) Normative or modulating property
2) Similarity with the "biological response modifiers"
3) Results achieved through microdoses
4) Therapeutic results depending on:
   a) dosage
   b) administration type
   c) administration time
   d) immune status.

▶ Moreover, PRM does not use units that have "**similarity** with the modifiers of the biological response" [point 2)].
It uses the **real** modifiers of the biological response - those that work physiologically at those concentrations!
- The rational inclusion in therapeutic practice of homeopathised CKs, hormones, neurotransmitters and homeopathised peptides at the same dilution in which they are physiologically present and active in the human body and the formulation of innovative medical products containing unitaries of which we know the active principles and their action in the healthy and sick person, define and are inherent to PRM, which does not deny the past but faces the future strong in the consciousness that it can always be updated and adapt to the new ideas and new solutions that science will provide. ■

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➤ **Tables 1, 2, 5, 6 are original by the Author; Tables 3, 4, are adapted explanations by the Author in relation to the updated bibliography.**

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