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FROM LOW-GRADE CHRONIC INFLAMMATION TO ACUTE INFLAMMATION – A CHRONOBIOLOGY OF THE INFLAMMATORY PROCESS

SUMMARY

In the last decade it has become increasingly clear that and how Low-Grade Chronic Systemic Inflammation is the common denominator of many severe diseases – both systemic and not – typical of the industrialized and of the rapidly developing countries. Such pathologies are based on the so-called "deadly quartet", i.e. overweight/obesity, impaired glucose homeostasis, arterial hypertension, and atherogenic dyslipidemia.

The genes once belonging to the Genus Homo were selected through a general and specific evolution, programmed for an Immune System which is about 2 million years old and which results unsuitable to the current lifestyle.

In most of the chronic diseases typical of the Western societies, Low-Grade Chronic Systemic Inflammation does not end due to suboptimal or over-maximal replies.

Exceeding nutrients and trash food result in a pathologic accumulation of fatty acids in the Adipose Organ, especially the subcutaneous, omental, perivisceral and intravisceral.
Man is not capable of converting fat, with the exception of glycerol, to sugars.

Subsequently the following phenomena occur: first hypertrophy, then hyperplasia of the adipocytes, with the interposition, among adipocytes, of macrophages gathered in the so-called crown-like structures. These macrophages are strictly related to the adipocyte death.
This is the first trigger towards Low-Grade Chronic Systemic Inflammation.

Here is proposed a biologic therapy to treat Low-Grade Chronic Systemic Inflammation with complex homeopathized low-dose medicines, physiological regulating medicines, and regulating nutraceuticals.

KEY WORDS

LOW-GRADE CHRONIC SYSTEMIC INFLAMMATION, METABOLIC SYNDROME, INSULIN-RESISTANCE, TYPE 2 DIABETES MELLITUS, EVOLUTIONARY MEDICINE, PALEOLITHIC MAN, *HOMO ERECTUS*

INTRODUCTION – *CAVEAT EMPTOR*

In the last decade it has become increasingly clear that **Low-Grade Chronic Systemic Inflammation** is the most important basis and the lowest common denominator of many serious diseases – systemic and not – characteristics of the industrialized countries or in the process of rapid development, centered on what has been called the "**deadly quartet**" (Kaplan, 1989): **upper-body obesity**, **glucose intolerance**, **hypertriglyceridemia**, and **hypertension**.

This combination of closely related, and often even interindependent clinical conditions are prodromal to Type 2 Diabetes Mellitus, cardiovascular diseases, some malignant neoplasms (eg. breast cancer, colorectal cancer, pancreas cancer), neurodegenerative diseases (Alzheimer 's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis - ALS), pregnancy complications (gestational diabetes, preeclampsia), fertility problems (PCOS).

- Pregnancy itself is considered to be a physiological state of Low-Grade Chronic Systemic Inflammation (Hanguel-de Mouzon *and* Guerra-Millo, 2006).

Low-Grade Chronic Systemic Inflammation determines insulin resistance and compensatory hyperinsulinemia, eventualities almost inevitable when you consider *Homo sapiens* himself is predisposed to metabolic inflammatory dysfunctions, unless he actively changes – drastically and forever – his lifestyle.

– *Caveat emptor*. "Let the buyer beware". Watch out.

Let him beware of junk food, of rich, elaborate and antigenic diet, of sweetened beverages which have replaced water, of long hours spent watching TV, playing videogames and using computers, of chronic stress, of negative actions and thoughts, but also of infections/inflammations which are unsolved, or only partially solved or solved disrespectfully of the timing set by chronobiology (e.g. suppressive pharmacologic therapies).

• Returning to the Paleolithic man's eating habits prevents and helps treating Low-Grade Chronic Systemic Inflammation and the wide range of conditions related to it.

Figure 1 ***Time Magazine*** **– Cover of the issue dated 23 February 2004. – The secret killer.**

It is not a matter of reviving J.J. Rousseau and his Myth of the *Noble Savage*.
- It is to limit – among others – the damage of 245 million people worldwide suffering from Type 2 Diabetes Mellitus, the most common form of diabetes usually occurring in the population over 40.

In particular, factors responsible of ≈ 90% of the cases of Type 2 Diabetes Mellitus are overweight /obesity (globesity, as defined by WHO), even if 23% of the obese shows no metabolic problem (Bonora *et* Al., 1998).

De Silva *and* Frayling (2010) and Smushkin *and* Vella (2010) identified several variants of the DNA sequence protecting from Type 2 Diabetes Mellitus: there is relevant evidence indicating that these genes produce important hormetic answers in pancreatic islets, liver and muscle.

Even high levels of bacterial endotoxins Gram - (lipopolysaccharide - LPS), chronic consumption of alcohol and cigarettes, periodontal diseases (Nakajima *and* Yamazaki, 2009) and age (inflammaging) appear to be responsible for the Low-Grade Chronic Systemic Inflammation that does not come to a solution.

- Increased lipid intake leads to the increase of LPS that, in addition to stimulating the incretion of pro-inflammatory messengers, has an inhibitory action on insulin (Shoelson *et* Al., 2006).

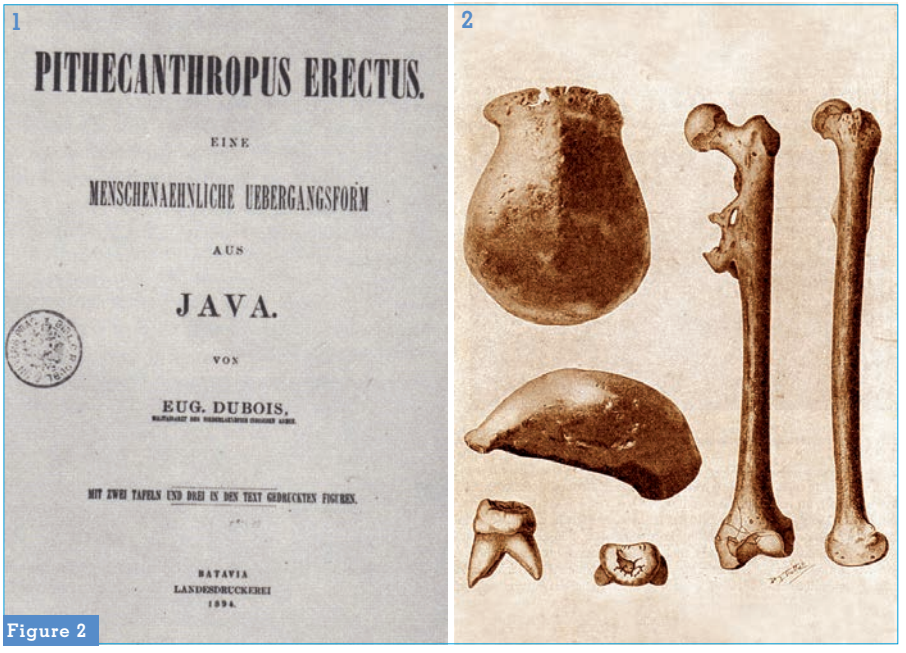


Figure 2

1) Cover of the descriptive publication on the discovery of *Pithecanthropus erectus*, Batavia; 1891.
2) The first of the two Tables included in the original publication.

A FAMOUS DIABETOLOGIST, THREE AMERICAN JOURNALISTS AND *PITHECANTHROPUS ERECTUS*

• **Gerald** "Jerry" **M. Reaven** (1928-), professor *emeritus* at the Stanford University School of Medicine, California - USA, published in 1988 an article in which it is defined and marked for the first time the concept of insulin resistance and its implications on the whole metabolic homeostasis: 12 pages on the prestigious scientific journal *Diabetes* that were to open new research opportunities and studies and were to revolutionize – some years later – the lifestyle of millions of people.
The publication followed his keynote lecture held at the *Banting Lecture* of the same year.

– The annual *Banting Lectures* are named after Frederick Banting (1891-1941) who, together with John Macleod (1876-1935), was awarded the Nobel Prize for Medicine and Physiology in 1923 for the discovery of insulin.

In 1988 the distinction between Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus had not yet been codified and – least of all – had Low-Grade Chronic Systemic Inflammation been put in close relation with Type 2 Diabetes Mellitus.

• *Time Magazine* (Monday, February 23, 2004) published the cover title "The secret killer. The surprising link between inflammation and heart attacks, cancer, Alzheimer's and other diseases. What you can do to fight it" (Figure 1).
The article of the three journalists **Christine Gorman**, **Alice Parker** and **Kristina Dell** begins with the following passage *"What does a stubbed toe or a splinter in a finger have to do with your risk of developing Alzheimer's disease, suffering a heart attack or succumbing to colon cancer?"*. And ends by saying *"If scientists are right — and the evidence is starting to look pretty good — it could radically change..."*.

– Researchers were right and evidence proved it.

Rogers (2008) was exemplary in saying: (…) *"head trauma may kill hundreds of thousands of neurons, but the secondary inflammatory response to head trauma may kill millions of neurons or the patient himself"*.

• **Eugène Dubois** (1858-1940), a young Dutch physician, anatomist, military surgeon in the Dutch East Indies and passionate about geology and paleontology, fascinated by the theories of Ernst Haeckel, Charles Darwin and Alfred Wallace, in search of the "missing link" (science has now abandoned the search of the missing link simply because it does not exist; during the evolution of Homo, more similar Genera coexisted, even in the same habitat or nearby habitats), discovered in 1890 in Java - Indonesia, at a muddy bend of the river Begawan [Trinil - Ngawi (Solo - currently Surakarta)] few fossil remains unquestionably "humanoid": a complete skull, a complete link femur, five small femoral fragments and a molar tooth, dating from the Middle Pleistocene (lower Paleolithic), which belonged to a male adult, defined and classified by Dubois as *Pithecanthropus erectus* (Dubois, 1915) (Figure 2).

– In the period 1937-1941 the German paleoanthropologist Gustav von Koenigswald (1902-1982) continues the research started by Dubois and discovered in Sangiran (now Sangiran Archaeological Site - Central Java, UNESCO World Heritage Centre) three large cranial fragments and several teeth definitely belonging to *Pithecanthropus erectus*, thus enriching the details concerning this extraordinary creature, a true milestone in the evolutionary path that led to *Homo sapiens* (von Koenigswald, 1937; von Koenigswald *and* Tobias, 1964).

Currently the name of Gen. Pithecanthropus (in Greek, ape man) is replaced with that of Homo (***Homo erectus***), testifying its belonging to Gen. Homo, that migrated between 1.8 and 1.3 million years ago from East Africa to Asia, and its upright (alternating bipedal walking).

– *Homo erectus* had a cranial capacity corresponding to only 60- 65% (**900 cm^3**) of that of *Homo sapiens* (**1450 cm^3**) (Figure 3); he used rudimentary stone tools and controlled fire.

The anatomy of his upper airways did not allow, nevertheless, to produce vocalizations similar to any articulated speech.

The skeletal anatomy of *H. erectus* was very similar (90%) to that of current *H. sapiens* (with more pronounced sexual dimorphism), but his brain was on average inferior (**550 - 600 cm^3**) compared to modern man's male average cranial capacity (the average values for the various racial groups , i.e. sub-continental human morphological variants, range between 1000 cm^3 and 1500 cm^3) (Figure 4).

– An anatomical and physiological huge gap, filled in a quick evolutionary time by *Homo heidelbergensis*, *Homo neanderthalensis* ... until today.

Human brain is now that of an oversized primate.

▶ What do a famous diabetologist, three young journalists from *Time Magazine* and a Paleolithic man have to do with each other?

– Nothing at all apparently, but in substance they have much to do, because the starting point of Low-Grade Chronic Systemic Inflammation lies in the fact of being ***Homo sapiens*... in the XXI century**.

An ancient genome adapted to the environment of 1.5 million years ago has arrived – almost unchanged – having to deal with a variety of different environments and climates, as well as the excesses of current lifestyles.

Figure 3

Graphic recreation of *Homo erectus*.
- In the frame, skull and cerebral compartment.

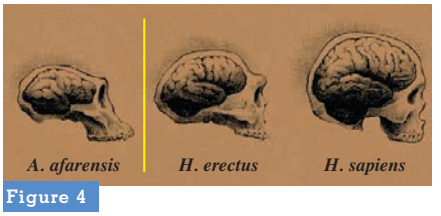


Figure 4

THE METABOLIC PHLOGOTYPOLOGY – AN OBESOGENIC LIFESTYLE

Genes belonging to Gen. Homo have been selected by the general (Class Mammalia) and specific evolution (Order Primates) and scheduled for an Immune System that is ill-suited to the current lifestyle of the industrialized countries.

– **Pro-inflammatory factors** of Western world's diet include:
over-consumption of saturated fatty acids, e.g. triglycerides found in animals / plants (meat, milkfat, butter, lard, coconut oil) (Jimenez-Gomez *et* Al., 2009); industrially produced trans fats (e.g. margarines) (Mozaffarian, 2006; Mozaffarian *et* Al., 2009); high ratio Ω6 / Ω3 (Serhan *and* Chiang, 2008; He *et* Al., 2009); low intake of Ω3 long-chain

polyunsaturated fatty acids in fish (Din *et* Al., 2004); low intake of Vit. D (Adorini *and* Penna, 2008), Vit. K (Shea *et* Al., 2008), Mg (Kim *et* Al., 2010); much-fat-low-fiber diet (Cani *and* Delzenne, 2010); carbohydrates with high glycemic index (Lihu *et* Al., 2002; Levitan *et* Al., 2008); unbalance pro oxidase / anti-oxidase (Vertuani *et* Al., 2004); low intake of vegetables / fruits (Pan *et* Al., 2009; Holt *et* Al., 2009).

Diet-related **indirect factors** are an anomalous composition of the bacterial flora of the oral cavity (Koren *et* Al., 2011), especially of the gums (Humphrey *et* Al., 2008; Takahashi *et* Al., 2010), of the bowel (Humphrey *et* Al., 2008; Koren *et* Al., 2011); patho stress / chronic distress (Black *and* Garbutt, 2002; Garcia-Bueno *et* Al., 2008), smoke + environmental pollution (Egger *and* Dixon, 2011).

- In most chronic diseases – if not in all (Ruiz Nunez *et* Al., 2013) – which are typical of Western society, the response to Low-Grade Chronic Systemic Inflammation does not end with suboptimal or above-maximum responses (Chiang *et* Al., 2012) (Table 1).

To make the situation envisaged by today lifestyle even worse contribute, among others: decreased physical activity (Petersen *et* Al., 2005; Huffman *et* Al., 2006; Petersen *et* Al., 2007; Roubenoff, 2008; Handschin *and* Spiegelman, 2008) and insufficient sleep (Dinges *and* Simpson, 2007; Irwin *et* Al., 2008; Mullington *et* Al., 2010).

– Although the Immune System of the XXI century *H. sapiens* is well-suited to cope with acute inflammation - an-

Table 1

Low-Grade Chronic Systemic Inflammation, apart from involving metabolism as a whole, causes effects concerning the following: Cardio-circulatory System, Osteo-arthro-myofascial System, Digestive System, Nervous System, and Immune System.
– Low-Grade Chronic Systemic Inflammation is also "guilty" of age-related inflammation, i.e. inflamm-aging.

giophlogosis (neutrophil / lymphocyte), it is partially "unprepared", "exposed", "mute" to solve the chronic inflammatory process, i.e. histophlogosis (macrophages, plasma cells), as well as – and above all – the low-grade one.

The bacterial flora has evolved with humans and is different in different human races: the bacterial flora of the Japanese – for example – is derived from marine bacteria (Hehemann *et* Al., 2010) and is unique to the Japanese (Koshiyama, 2010).

Helminths and bacteria have further contributed to the development of Innate Immunity.

– Exceeding free fatty acids (FFA) released by the Adipose Organ silence the Toll-like receptors (TLR) of the Innate Immunity cells and stimulate inflammatory responses of the macrophages (see below): the **Low-Grade Chronic Systemic Inflammation is the result of an Immune System that does not stops** (in loop), **because stimulated constantly**.

The enormous and rapid brain development during the evolution of the "Naked Ape" (as in *The Naked Ape* by D. Morris, 1967), fully explains the evolution of man and his radical impact on the external (and internal) environment.

The brain size is correlated to the number of neurons (Azevedo *et* Al., 2009; Herculano-Houzel, 2010; Gabi *et* Al., 2010) and intelligence (Deaner *et* Al., 2007).

– *Homo sapiens* and the living chimpanzees (*Pan troglodytes* Blum., 1775; subspecies) and bonobos (*Pan paniscus* Schwarz, 1929; subspecies) share a common ancestor who lived in Africa ≈ 5 to 6 million years ago.

In the last 2.5 million cranial capacity of Prehominids increased from 400 cm^3 ≈ (as in *Australopithecus afarensis*, in adult chimpanzees, and in the human infant) to 1450 cm^3 ≈ (Figure 5).

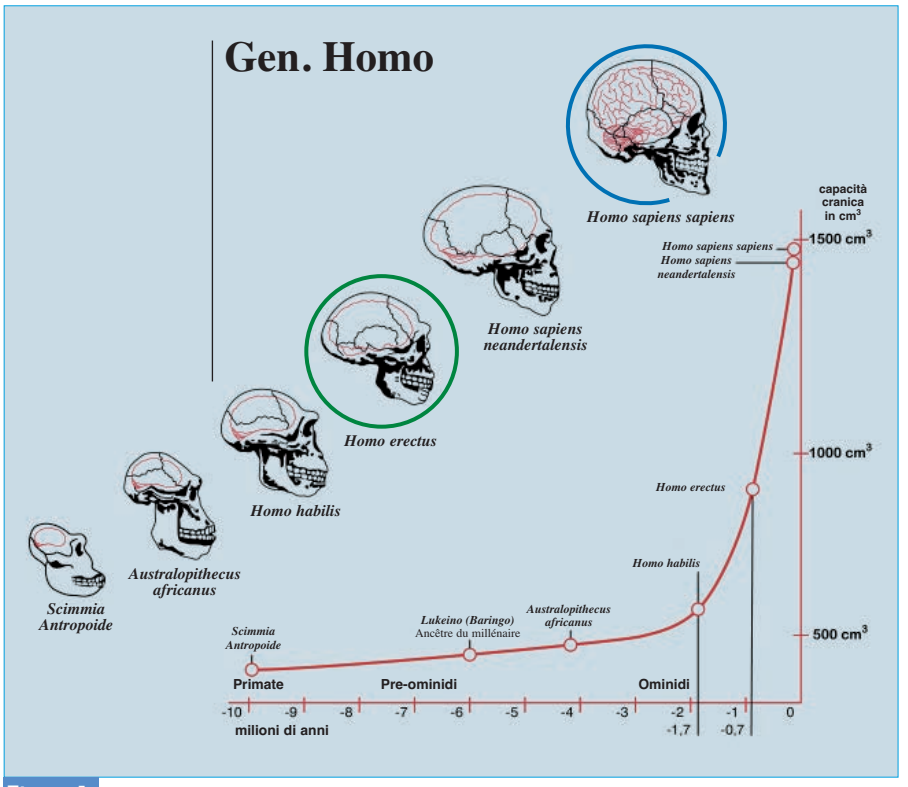


Figure 5

Cranial capacity of some Pre-Hominids, Hominids and Homo. The *Typus* of *H. erectus* (Trinil) and the other *H. erectus* discovered in Java have an average cranial capacity of 800 cm^3. – The other known *H. erectus* (e.g. *H. erectus pekinensis* – discovered in Zhoukoudian- China) had a greater cranial capacity (950 cm^3).

▶ This extraordinary encephalization was possible thanks to the procurement of **high-quality foods** such as eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA) [fish] and Iodine, Selenium, Iron, Vitamins A and D, etc., all easily accessible in a **land and water ecosystem** (Broadhurst *et* Al., 1998; Broadhurst *et* Al., 2002; Muskiet *and* Kuipers, 2010).

– These are **brain selective** nutrients and exhibit – even today – the largest insufficiency in the world.

These nutrients are expensive both in economic terms and due to the effort made to acquire them.

The agricultural revolution (10,000 years ago) and the industrial revolution (250 years ago) with their food mass, different productions have engendered a deep discrepancy and progressive lack of "understanding" between our ancient genome and the current lifestyle.

The human brain **consumes 25% of all the basal metabolism** (Aiello *and* Wheeler, 1995; Leonard *et* Al., 2003; Brown *et* Al., 2004; Muskiet, 2005), the liver 18%, the hollow organs of the gastro-intestinal tract 15%, and the skeletal muscle 15%.

The human brain alone consumes such a large amount of glucose / day (≈130 gr/day).

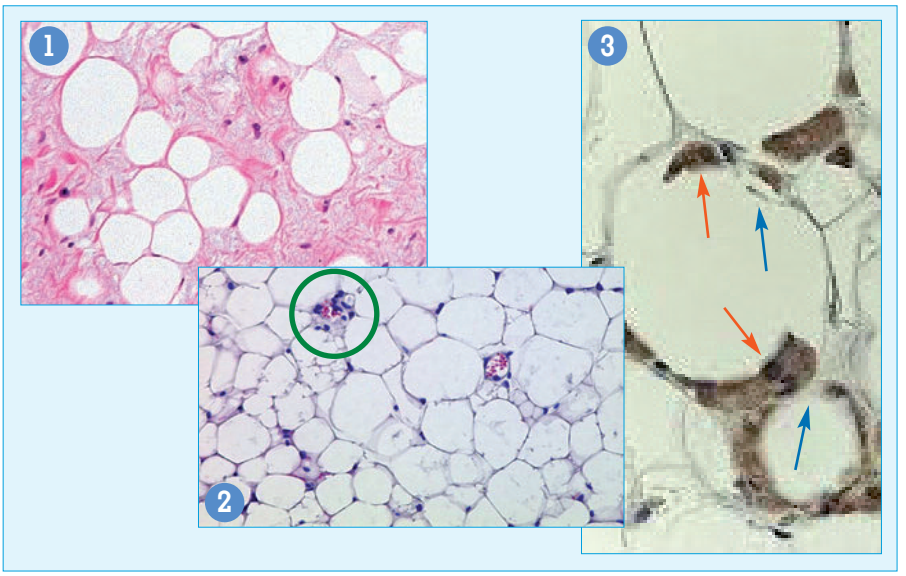
The frontal cortex is the most sensitive to the blood level of glucose.

– The chimpanzee, which shares 97% of the human genome (The Chimpanzee Sequencing and Analysis Consortium, 2005), consumes less than 10% of their basal metabolism to run its brain.

– **Energy reserves allocated to the brain** must remain **stable**, even during periods of food deprivation: the other organs are to pay for the consequences, which explains very well how the first weight loss

Figure 6

Endocrine Adipose Organ.
– Adipocytes:
1 Hypertrophy; 2 Hyperplasia.
In the circle, macrophage clusters "crown-like structures";
3 Each macrophage cluster is made of 10-12 cells on average.
– In 3) it can be seen some polynuclear macrophages (red arrows), and the initial damages of the cell wall of the adipocyte (blue arrow).



during forced or wanted food restriction is at the expense of the lean mass, and not of fat mass.

This also explains the "thin-fat baby", born from an underfed mother during gestation (Yajnik *et* Al., 2003).
The thin-fat child has poor lean mass and abundant fat mass; he is an overweight child affected by sarcopenia.
– The thin-fat child presents hyperglycemia at birth and will develop insulin resistance syndrome, if he will live in an obesogenic environment.

The reduced intake of carbohydrates during the evolution from only vegetarian omnivores made man highly dependent on **amino acids** (meat, fish, legumes) **as source of gluconeogenesis**.

▶ It is the human brain with its energy requirements to steer toward insulin resistance.

– Type 2 Diabetes Mellitus confirms this.

The inflammatory transduction signal causes the inhibition of the postreceptorial pathway for insulin, thus producing insulin resistance (de Luca *and* Olefsky, 2008).
Insulin resistance and compensatory hyperinsulinemia produced by Low-Grade Chronic Systemic Inflammation is **deeply rooted** in the evolution of *Homo sapiens*.

– It doesn't take much to start and maintain it.
Some genotypes that were advantageous under certain situations, are disadvantageous in other (trade-off).

Insulin resistance syndrome defined by Reaven in 2005 is - in essence - a syndrome due to **energy re-allocation**.

Low-Grade Chronic Systemic Inflammation should be defined, more appropriately, Chronic Systemic Inflammation of Low-Grade induced by energy re-allocation.
Low-Grade Chronic Systemic Inflammation determines:

– Reduced insulin sensitivity (redistribution of glucose and lipids, hypertension);
– Increased Sympathetic Nervous System activity (stimulation of lipolysis,

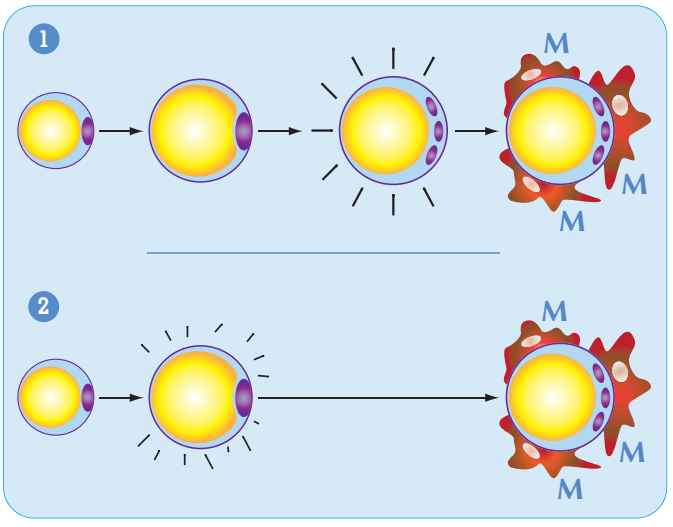


Table 2

Hypertrophy / hyperplasia of the adipocyte – possible mechanisms responsible for the peri-adipocyte "crown-like structure" formation, syncytia including up to 10-12 macrophages (M).
1) Hypertrophy leads the adipocyte to death; its cellular remains attract macrophages.
2) Hypertrophy / hyperplasia causes the secretion of chemoattractors, enrolling the macrophages around the adipocyte, and the adipocyte lysis.
-The macrophages start Low-Grade Chronic Systemic Inflammation.

glyconeogenesis and glycogenogenesis);
– Increased tone of HPA (Hypothalamic-Pituitary-Adrenal) Axis; poor increase in cortisol, glyconeogenesis with resistance to cortisol in the Immune System;
– Decreased HPG (Hypothalamic-Pituitary-Gonadal) Axis and consequent sarcopenia, androgen / estrogen imbalance, inhibition of sexual activity and reproduction;
– Sickness behavior (energy saving; hypersomnia; low muscle, brain and intestine activity).

GLUCOSE → GLUCOSE-DEPENDENT ORGANS [especially BRAIN]

GLUCOSE **PLUS** → STORAGE IN THE LIVER AND MUSCLE (GLYCOGEN)

GLUCOSE **SURPLUS** → ABDOMINAL FAT /FATTY LIVER → **INSULIN-RESISTANCE**

Insulin resistance leads to a lower entry of glucose in neurons, which continue to "work" thanks to the energy derived from **protein catabolism** and **ketones** from fatty acids (acetone, acetoacetic acid, β-hydroxybutyric acid) ...
... exactly as it happened in the Paleolithic *Homo erectus* when foods highest in glucose were scarce, probably only wild honey, rare wild fruits and tubers and animals' liver, thus forcing him to draw energy for his brain – and his evolution – from proteins and fats of animal origin (hunting, fishing, collection of insect larvae).

These activities – which are performed necessarily by a group – favored the social organization, the intraspecific hierarchy and the articulated speech.

– No coincidence that specific tribes – for example the Mangyan from Mindoro - Philippines, the Yanomamö from Orinoco or the Asmat from Papua - New Guinea – living in general conditions which are more similar to those of the Paleolithic Man than to those of the capitals of the countries where they live, do not suffer from metabolic syndrome / insulin resistance.
They do not suffer from its consequences either: they live and feed themselves as the Paleolithic *H. erectus*.

During the process of Low-Grade Chronic Systemic Inflammation metabolic adaptation signals are transmitted by the **pro-inflammatory cytokines**.

– The resulting insulin resistance determines – as shown above – energy reallocation.

It is hyperinsulinemia to determine those damages which are part of a "general picture" called Metabolic Syndrome (in the muscle: reduced storage of glycogen = easy fatigability; in the adipose organ: increased hydrolysis of triglycerides and their mobilization as glycerol and free fatty acids = rise of cardiovascular risk).

The excess of "unfit" nutrients turn out in a pathological accumulation of fatty acids (triglycerides) in the adipose organ, especially subcutaneously and omentally, periviscerally and intraviscerally.

Man is not capable of converting fat to sugars, with the exception of glycerol.

▶ The first phenomenon to be produced is the adipocyte hypertrophy (Brook *et* Al., 1972), then adipocyte hyperplasia (in Hausman *et* Al., 2001; *in* Cinti, 2005), with the interposition, among the adipocytes, of macrophages thickened in clusters to constitute the so-called ***crown-like structures*** (Figure 6).

– These macrophages are closely related to the adipocyte death.

The hypertrophic / hyperplastic growth of the adipocytes causes insufficient blood supply and consequent hypooxygenation (Wood *et* Al., 2009), followed by alteration / disintegration and death (Weisberg *et* Al., 2003; Duffault *et* Al., 2009).

Unstructured / dead adipocytes secrete on one hand MCP-1 (Monocyte Chemotactic Protein-1), a protein that attracts macrophages *in situ* and consequent macrophage infiltration of the Adipose Organ (Kanda *et* Al., 2006) (Author's note: they are the macrophage clusters "similar to a crown"), and on the other the MIF-1 and -2 (Macrophage Migration Inhibitory Factor -1, -2) through the activation of a gene that expresses cell-mediated immunity, the same involved in systemic juvenile rheumatoid arthritis (JRA) [MIM: 604302] (Fincane *et* Al., 2012) (Table 2).

It is the overcoming of the "critical dimension" [the surface of the cell membrane squares (... ^{2}); the cell volume cubes (... ^{3}) = little exchange surface for much volume to nourish] and the consequent state of cellular hypoxia which sacrifices the adipocyte.

– This is the trigger, the primary cause of Low-Grade Chronic Systemic Inflammation.

The recruited macrophages belong to two morphotypes:

M1 *"Typically activated"* **+** → inflammation.

M2 *"activated alternatively"* **–** → inflammation; the **1st** attempt the organism makes to limit the inflammatory cascade.

As mentioned, in the problematic sites for the adipocytes, M1 are arranged to form clusters, syncytia up to 10-12 cells. There are also giant mononuclear cells, characteristic of chronic inflammation.

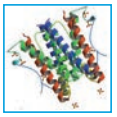
▶ From this moment onwards, the mechanism of the deadly cascade, of the perverse axis, is triggered. -The Axis of Evil (Table 3):
The Adipose Organ frees those messengers responsible for the onset of severe diseases resulting from Low-Grade Systemic Inflammation.

It is hypertrophy / hyperplasia of endoabdominal adipocytes to induce Low-Grade Chronic Systemic Inflammation, the real mother of all diseases and chronoaging.

THE PERVERSE AXIS

Basically the perverse axis is supported by:

IL-6 ↑



It has a recognized role in the genesis of:

– Type 2 Diabetes Mellitus (Kristiansen *and* Mandrup-Poulsen, 2005);
- Atherosclerosis (Huber *et* Al., 1999);
- Prostate cancer (Smith *et* Al., 2001);
- Rheumatoid arthritis (Nashimoto, 2006);
- Post-menopausal osteoporosis, due to the stimulation of the osteoclasts (Theoharides *et* Al., 2002);
- Alzheimer's disease (Swardfager *et* Al., 2010);
- Behçet's disease (Hirohata *and* Kikuchi, 2012);
- Depression (Dowlati *et* Al., 2010; Capuron *et* Al., 2011);
- Epigenetic effects on the CNS (Foran *et* Al., 2010).

Recently Mauer *et* Al. (2014) have demonstrated partial inhibition of the low-grade inflammatory state by IL-6, showing an effect of bipolar modulation and thus highlighting the nature of the context and the pattern in which the CKs operate.

This is the **2nd** attempt the organism makes to limit the pro-inflammatory cascade.

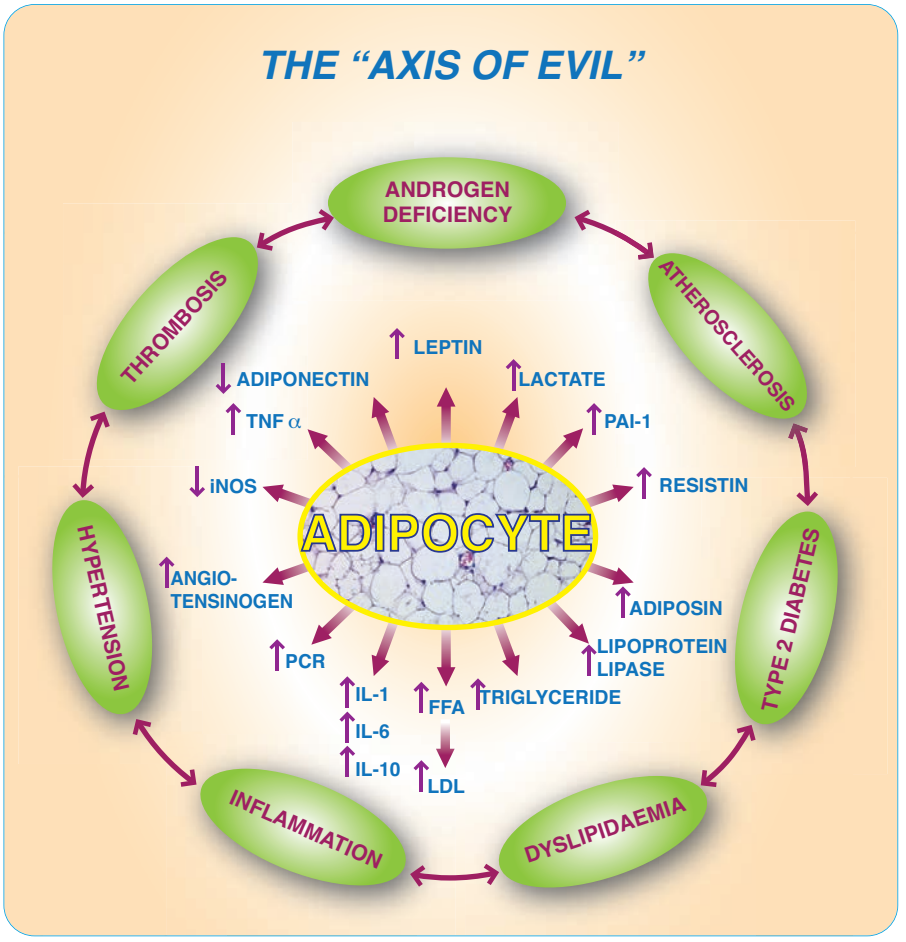


Table. 3

The Axis of evil.

- Hyperplasia of the adipocyte, especially omental, perivisceral and intravisceral, and its cytolysis; it triggers a number of increases and decreases of messenger molecules causing Low-Grade Chronic Systemic Inflammation, Type 2 Diabetes Mellitus, dyslipidemia, atherosclerosis, hypertension, thrombosis/embolism and androgenic deficit.

IL-1 SUPERFAMILY ↑

The IL-1 Superfamily consists – today – of 11 CKs, especially IL-1α; IL-1β; IL-1Ra; IL-18; IL-37; IL-38.

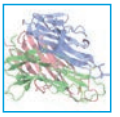
The mechanism of action of IL-1 is known (Dinarello, 1988; 2002): basically it has a vasodilator effect, thanks to the stimulation of Prostaglandin E1 (mainly), COX-1 and -2 (mainly) and nitric oxide (NO).

– It is on these servo systems that corticosteroids, NSAIDs and acetylsalicylic acid act therapeutically, inhibiting them.

An important role in controlling Low-Grade Chronic Systemic Inflammation is also played by IL-37, certainly anti-inflammatory, and by IL-38, probably anti-inflammatory.

These two cytokines are the **3rd** attempt the organism makes to control the pro-inflammatory cascade.

TNF-α ↑



TNF-α has a general role in regulating the Immune System.

Together with IL-1, it stimulates in the liver the acute-phase proteins.

– It induces insulin resistance (Nieto-Vazquez *et* Al., 2008);
- It increases the catabolism of striated muscles [metabolic sarcopenia (Phillips *and* Leeuwenburg, 2005)];
- It lowers the levels of adiponectin (Lihu *et* Al., 2005).

Adiponectin (see below) promotes the oxidation of fatty acids in the muscles, it reduces its flow to the liver, and reduces the production of glucose by the liver.

Lowering the levels of adiponectin induced by TNF-α leads "fat" to the muscle, the liver and increases the liver glycogen reserves.

▶ The patient suffering from Type 2 Diabetes Mellitus may present glycemia higher in the morning than 2 hours after dinner.

- In 10 hours of overnight fasting the patient may experience hypoglycemia.

Any compensatory hyperglycemia at night is due to the hepatic reserves of glucose, not from any other source.

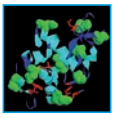
TNF-α also has a well-known role in the genesis of:

– Neoplasms (Locksley *et* Al., 2001);
– Alzheimer's disease (Swardfager *et* Al., 2010);
– IBDs (Brynskov *et* Al., 2002);
– Depression (Dowlati *et* Al., 2010);
– Premature aging (intellectual laxity, reduced motivation, pessimism, anorexia, memory decline, cognitive decline, sickness behavior) (Grohol, 2011);
– Sarcopenia (Cruz-Jentolft *et* Al., 2014);
– Osteoporosis (McCormick, 2007);
– Gluten Sensitivity;
– ASD-Autistic Spectrum Disorders (Rossignol *and* Frye, 2012);
– ASD with mothers affected by Low-Grade Chronic Systemic Inflammation (Harrison, 2013).

IL-10 ↑

IL-10, an anti-inflammatory cytokine, acts on the pro-inflammatory effectors thanks to the action of at least 10 messenger molecules (Table 4).

LEPTIN ↑



– When a **normal-weight** subject fattens, the adipose organ produces leptin → reduced sense of hunger (hypothalamus).
– When an **overweight-obese** subject fattens, the adipose organ produces leptin, but this stimulus is ignored due to altered hypothalamic sensitivity.

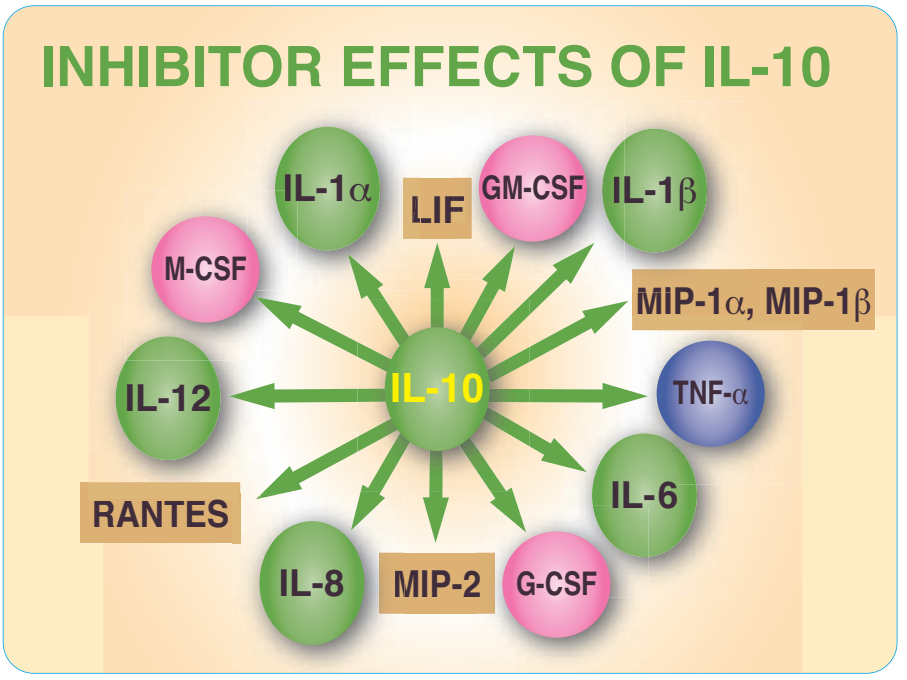
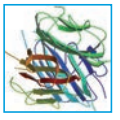


Table 4

IL-10 – Inhibitor effects of inflammation (and others), due to the stimulating or inhibiting action of: LIF (Leukemia Inhibitory Factor), M-CSF (Macrophage-Colony Stimulating Factor), G-CSF (Granulocyte-Colony Stimulating Factor), GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor), MIP (Macrophage Inhibitory Protein) 1 (α ; β) e 2, RANTES – Cytokines of the IL-8 SuperFamily; IL-1α, IL-1β, IL-6, IL-8, IL-12, TNF-α.
– IL-10, a classic anti-inflammatory cytokine, presents pleiotropism and generates different actors to modulate the response of the so-called "fire inside".

ADIPONECTIN ↓
(Adipose Organ and Muscle Tissue)



The concentrations of adiponectin are inversely proportional to Body Mass Index (BMI).
The action, the regulation and the association with insulin sensitivity were defined by Lihu *et* Al. (2005).
It was demonstrated the protective role of adiponectin in the fatty liver disease (FLD) (Wang *et* Al., 2009).

– The deficiency of adiponectin has a recognized role in the genesis of colorectal cancer (Fujisawa *et* Al., 2008).

SYSTEMIC LOW-GRADE CHRONIC INFLAMMATION – A BIOLOGICAL THERAPY

In addition to a healthy diet, relatively low in carbohydrates and lipids, with appropriate sufficient protein intake (from fish, white meat, legumes and oilseeds), fresh vegetables and fresh fruit poor in sugar, adequate movement and moderate daily aerobic exercise (Pelosi, 2014):

A) GENERAL THERAPY

– *TO SUPPORT*

1) INTRACELLULAR METABOLISM

• Guna-Cell, 10 drops, 3 times daily (3 times weekly).

2) EXTRACELLULAR METABOLISM

• Guna-Matrix, 10 drops, 3 times daily + Guna-Lympho, 10 drops, 3 times daily (3 times weekly).

– *TO CONTRAST*

1) LOW-GRADE CHRONIC SYSTEMIC INFLAMMATION

• Guna-Flam, 10 drops, 3 times daily +
• Guna-Anti IL1 4CH, 10 drops, 2 times daily +
• Guna-TGF β1 4CH, 10 drops, 2 times daily +
• Guna-Interleukin 10 4CH, 10 drops, 2 times daily.

– The latter 2 PRM cytokines lower the pro-inflammatory side of the immune scale.
– IL-10 also works on the physiological circadian re-modelling of the extra-cellular matrix, therefore supporting exchanges to and from the cell.

2) METABOLIC ACIDOSIS

• Gunabasic, 1 sachet daily.

The General Therapy is to be adopted for 1 month; stop for 2 months; a new course for 1 more month: 2 courses yearly.

B) SPECIFIC ORGAN-FUNCTION THERAPY

1) LIVER PROTECTION

• Guna-Liver pellets.

– In Guna-Liver some intermediate metabolitic coenzymes of the Krebs Cycle and the synthesis of pyrimidine support the *re-start* of the carbohydrate metabolism, and the synthesis of intrahepatic and intramusclular glycogen.

2) INTESTINE PROTECTION

• Colostro Noni, sachets.
• Eubioflor, drops.

3) ENERGETIC-METABOLIC SUPPORT
• Omeosport, pellets.

4) ANTIOXIDANTS

5) PSYCHO-MENTAL SUPPORT
• Guna Serotonin D6, drops.

The daily dosage and the length of therapy including medicines /nutraceuticals as in B) SPECIFIC ORGAN-FUNCTION THERAPY may change and are selected according to the inflammatory condition of every single patient.

CONCLUSIONS

The fossil remains of Java Man - *Homo (Pithecanthropus) erectus* discovered by Dr. Dubois in 1890-1, the Typus of the *erectus* to date, are kept in a small safe in the Dutch Museum of Natural History in Leiden, and exhibited to the public .

Those exposed in the *Museum Nasional Indonesia* in Jakarta are perfect resin copies, virtually indistinguishable from the originals.

... The femur looked anatomically modern, although during life it had suffered a severe injury complicated by osteomyelitis, healed and with well-established outcomes; yet it had belonged to an individual who had lived at least 1 million years ago.

I thought of Eugène Dubois, his vicissitudes after his return home following the extraordinary discovery that would open the way for Paleoanthropology, ... of my visit to the Sangiran Site three years before, where von Koeningswald had found other *H. erectus*. ..of the difficult nomadic life led by the Man of Java, ... of the possible causes of his death: lightning, a viral or bacterial disease, a rival in the hunting / fishing areas, a gang war, a predatory animal, maybe he drowned.

All these were and are conjectures, hypotheses that no one will ever be able to confirm or deny.

– His killer was neither **secret** nor **silent**.

– What is certain is that the Java Man did not die for acute myocardial infarction or pulmonary embolism, or for colorectal cancer.
– These dramatic events were to happen to the civilized *Homo sapiens*, now far from selective pressure, 1 million years later. ■

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See also:

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Figure 1
http://img.timeinc.net/time/magazine/archive/covers/2004/1101040223_400.jpg
Figure 2 (1)
http://upload.wikimedia.org/wikipedia/commons/7/75/Eugene_Dubois,_book.jpg
Figure 2 (2)
http://it.wikipedia.org/wiki/Uomo_di_Giava#mediaviewer/File:Pithecanthropus-erectus.jpg
Figure 3
http://fotolia.com
(#46391141 - Homo Erectus Portrait © AlienCat)
Figure 3 (thumbnail)
http://upload.wikimedia.org/wikipedia/commons/e/ea/Java_man.jpg (graphic processing by the author).
Figure 4
http://goldendome.org/EvolutionOfMan/BrainSize.jpg
Figure 5
http://www.pensierocritico.eu/files/brainEvolution2.jpg (translation and graphic processing by the author)
Figure 6 (1)
http://histologyolm.stevegallik.org/node/97
Figure 6 (2)
http://www.med.upenn.edu/ahimalab/images/White-adipose-tissue.jpg
Figure 6 (3)
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IL-6 (p.36)
http://old.sinobiological.com/cytokines/Interleukin/Crystal-Structure-of-Human-Interleukin-6.jpg
IL-1α [IL-1 SuperFamily] (p.36)
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TNF-α (p.36)
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LEPTIN (p.37)
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ADIPONECTIN (p.37)
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Table 1:
http://1.bp.blogspot.com/-0SOkLpaTeQ8/UxcdY92_EVI/AAAAAAAAHKQ/K04rw9DMouw/s1600/Chronic_Inflammatory_Demyelinating_Polyneuropathy-3.jpg (translation and graphic processing by the author).
Table 2: graphic processing by the author.
Table 3: translation and graphic processing by the author.
Table 4:
http://ipj.quintessenz.de/ipj/content/2001-01/poster67/fig1kl.jpg (graphic processing by the author).

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