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 – both systemic and not – typical 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 interdependent clinical conditions are prodromal to Type 2 Diabetes Mellitus, cardiovascular diseases, some malignant neoplasms (e.g. breast cancer, colorectal cancer, pancreatic 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.
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 homeotic 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 (inflamm-aging) 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 secretion of pro-inflammatory messengers, has an inhibitory action on insulin (Shoelson et al., 2006).

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 have not been yet codified and – least of all – had Low-Grade Chronic Systemic Inflammation been put in close relation with Type 2 Diabetes Mellitus.

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...”.

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.

Figure 1. Time Magazine – Cover of the issue dated 23 February 2004.

Figure 2. The secret killer.

- The secret killer.
– 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 Koenigswald, 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) continued the research started by Dubois and discovered in Sangiran (now Sangiran Archaeological Site - Central Java, UNESCO World Heritage Centre) three large cranial fragment and seven other 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, 1915; 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.

– 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 $\omega_6$ / $\omega_3$ (Serhan and Chiang, 2008; He et Al., 2009); low intake of $\omega_3$ 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-
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 Pre-Hominids increased from 400 cm³ ≈ (as in Australopithecus afarensis, in adult chimpanzees, and in the human infant) to 1450 cm³ ≈ (Figure 5).

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 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.

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.

– 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
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.

Type 2 Diabetes Mellitus confirms this.

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.

- 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,
glycogen metabolism and glycogen synthesis;
- Increased tone of HPA (Hypothalamic-Pituitary-Adrenal) Axis; poor increase in cortisol, glycogenesis 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 Yanomamó from Ori noco 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 omental, periviscerally and intraviscerally.

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.

**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 (Li-hu 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-Jentoft 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).

**LEPTIN**

When a normal-weight subject fattens, the adipose organ produces leptin, but this stimulus is ignored due to altered hypothalamic sensitivity.

When an overweight-obese subject fattens, the adipose organ produces leptin → reduced sense of hunger (hypothalamus).

**ADIPONECTIN**

The concentrations of adiponectin are inversely proportional to Body Mass Index (BMI).

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 metabolite coenzymes of the Krebs Cycle and the synthesis of pyrimidine support the re-start of the carbohydrate metabolism, and the synthesis of intrahepatic and intramuscular glycogen.

2) INTESTINE PROTECTION

- Colstro 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 Eugene Dubois, his vicissitudes after his return home following the extraordinary discovery that would open the way for Paleanthropology, ... 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 riddle 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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IL-6 (p.36) http://old.sinobiological.com/cytokines/Interleu-
kin/Solution-Structure-of-Human-Interleukin-1-pha.png

Figure 6 http://upload.wikimedia.org/wikipedia/commons/9/9b/Mouse_Tumor_Necrosis_Factor_Al-
pha.png
LEPTIN (p.37)
http://www2.dq.fct.unl.pt/cadeiras/qpn1/molweb2003/Leptina/leptin3D.gif

ADIPONECTIN (p.37)
http://upload.wikimedia.org/wikipedia/commons/1/13/PBB_Protein_ADIPOQ_image.jpg

Table 1: http://1.bp.blogspot.com/-0SOkLpaTeQ8/UxcdY92EVI/AAAAAAAAHKQ/K04rw9DMouw/s1600/C:
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/poster67fig1ki.jpg (graphic processing by the author).

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FDA listed and regulated 1

GUNA®-LIVER
HOMEOPATHIC MEDICINE

Drug Facts

Active Ingredients Purpose
Carduus marianus 2X Detoxification
Canthium americanus 6X Detoxification
Chelidonium majus 2X Detoxification
Chimaphila umbellata 6X Pain Reliever
Cislium 4X Stimulates Digestion
Cocculus 4X Antioxidant
Fumaricum acidum 4X Antioxidant
Gall bladder 8X Stimulates Digestion, Injuries 6X Stimulates Digestion
Inositol 6X Stimulates Digestion
Acidum 8X Stimulates Digestion
Kali sulphuricum 6X, 8X, 12X Stomach Activity
Lactobacillus ruminans 6X Stimulates Digestion
Lyposodium clavatum 6X Laxative
Natrum salicylicum 6X Antioxidant
Niacin pyrophosphate 4X Antioxidant
Natrium 6X Metabolic Support
Pulsatilla 8X Stimulates Digestion
Pulsatilla hydrochloricum 6X Antioxidant
Riboavitamin 6X Antioxidant
Saccharum officinarum 8X Laxative
Titanium hydrochloricum 6X Antioxidant

Uses: For the temporary relief of symptoms of colic and gas pains such as bloating, general aches and pains.

Directions:
• Turn tube upside down and rotate cap to release pellets into cap.
• Unscrew cap and without touching pellets tip them into the mouth under the tongue.
• Allow to dissolve.
• Take 15 minutes before meals.

Adults and children 12 years and older 5 pellets 3 times per day
Children between 12 years and 6 years of age 3 pellets 3 times per day
Children under 6 years and under 1 pellet 3 times per day to be dissolved into a little water

Warnings: Stop use and ask doctor if symptoms of bloating, aches and pains persist more than 3 days, or if fever develops. If pregnant or breast-feeding ask a doctor before use. Keep this and all medicines out of reach of children.

Package: Net Wt. 8 g/0.28 oz. 2 Tubes

Inactive Ingredient: Sucrose
Contacts: info@gunainc.com, tel. (484) 223 3500
www.gunainc.com

Other Information: Store at 20°-25°C (68°-77°F).

1 U.S. Food and Drug Administration Sec. 400.400 Conditions Under Which Homeopathic Drugs May be Marketed (CPG7132.15).

These statements have not been evaluated by the Food and Drug Administration. They are not intended to diagnose, treat, cure, or prevent any disease. They are not a substitute for individual medical attention.

US Distributor: GUNA® Laboratories
Gastroenterology

GUNA®-LIVER
PHYSIOLOGICAL REGULATING MEDICINE

Detoxification

Gastroenterology