

*The adipose tissue in the human body is there
for the best, the bad and the worse!*

**Paraphrased from Charles Lapiere
and Erik Maquoi (1)**

IN THE HEART OF ADIPOBIOLOGY: CARDIOMETABOLIC DISEASE

A report of the 2nd International Symposium on Adipobiology and Adipopharmacology (ISAA), 23-25 October 2009, Varna, Bulgaria

***George N. Chaldakov¹, Marco Fiore², Anton B. Tonchev¹, Gorana Rančić³, Mariyana G. Hristova⁴,
Neşe Tunçel⁵, Dimitar D. Kostov⁶, Vesselka Nikolova⁷, Vladmila Bojanić⁸, and Luigi Aloe²***

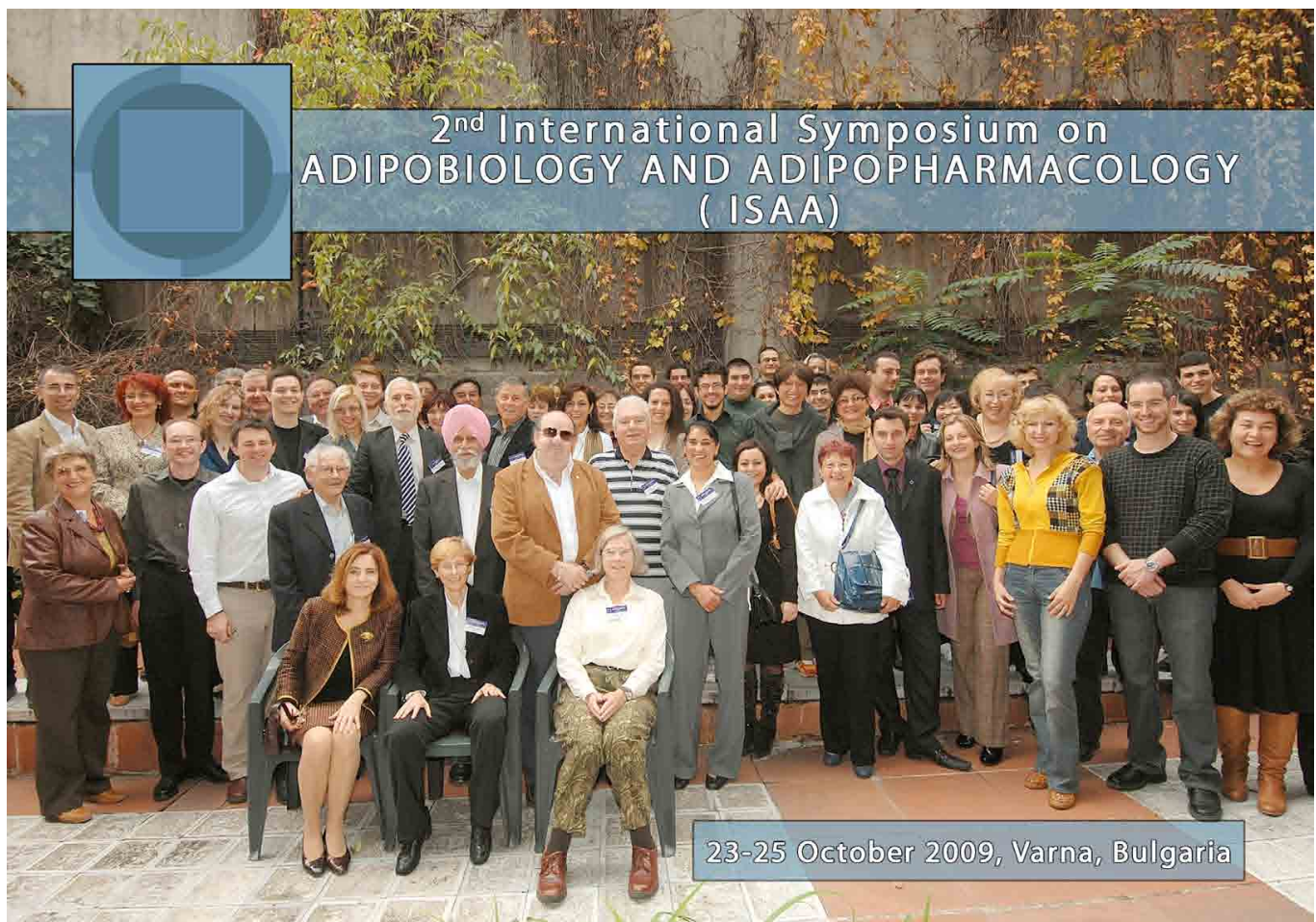
*¹Division of Cell Biology, Medical University, Varna, Bulgaria, ²Institute of Neurobiology and Molecular
Medicine, National Research Council-European Brain-Research Institute, Rome, Italy, ³Department of
Histology and Embryology, Niš University Medical Faculty, Niš, Serbia, ⁴Department of Endocrinology,
Private Policlinic, Varna, Bulgaria, ⁵Department of Physiology, Medical Faculty, Eskişehir Osmangazi
University, Eskişehir, Turkey, ⁶Department of Internal Medicine, University St Marina Hospital, Varna,
Bulgaria, ⁷Intensive Cardiology Unit, University St Marina Hospital, Varna, Bulgaria, and ⁸Department
of Pathophysiology, Niš University Medical Faculty, Niš, Serbia*

Published on 1 December 1994 issue of *Nature* (2), the Jeffrey Friedman's discovery "gave *leptin* in the beginning" of the endocrine saga of adipose tissue. Onwards, studies on this tissue have enjoyed an explosive growth that conceptualized a novel field of research, adipobiology (3). Arguably, in the heart of adipobiology and adipopharmacology are studies focusing on the pathogenesis, prevention and therapy of cardiometabolic diseases (CMD) including atherosclerosis, hypertension, obesity, type 2 diabetes, metabolic syndrome (global cardiometabolic risk), and lipodystrophies.

The 2nd International Symposium on Adipobiology and

Adipopharmacology (ISAA) was organized by the Bulgarian Society for Cell Biology. Scientists from 15 countries presented 34 state-of-the-science (SOS) lectures.

Gema Frühbeck (Pamplona, Spain) highlighted the significance of adipokines represented by a large number of signaling proteins, e.g. pro- and anti-inflammatory interleukins, also leptin, adiponectin, resistin, tumor necrosis factor- α , renin, angiotensin II, and the "newcomers" retinol-binding protein-4, angiopoietin-like protein-2 (Angpl-2) and Angpl-4 (fasting-induced adipose factor), visfatin, vaspin, pigment epithelium-derived factor, apelin, chemerin, adrenomedullin,



lipocalin-2, and nerve growth factor (NGF) (4). She also introduced caveolins and aquaporin-7 (AQP-7) into the pathogenesis of CMD.

Caroline Pond (Milton Keynes, UK) presented her SOS on paracrine interactions between perinodal white adipose tissue and lymph nodes. She demonstrated that adipocytes associated with lymphoid structures are specialised to supply fatty acids, and possibly other precursors, to lymphoid cells. Such mechanisms emancipate the immune system from fluctuations in the composition and quantity of dietary lipids and are particularly important during immune responses, when perinodal adipose tissue remote from the site of immune stimulation as well as that around the locally stimulated nodes are activated. Caroline Pond also provided evidence that defective perinodal adipose tissue may be central to Crohn's disease (5).

Harold Sacks (Memphis, Tennessee, USA) presented results about paracrine secretion of adipokines by epicardial adipose tissue and its significance for cardiovascular disease

(6). His talk as well as that of Caroline Pond stressed the relevance of adipotography in pursuing a hidden *Homo obesus* (7), a phenotype of TOFI (thin outside, fat inside), a term coined initially by Jimmy Bell (Imperial College, Hammersmith Hospital, London, UK), to emphasize that we cannot not rely only on BMI and other "classical" anthropometric measurements when imaging techniques (ECHO, MRI, PET) currently are able to provide visual information on external (outside) and internal (inside) accumulation of adipose tissue.

Stuart Wood (Liverpool, UK) explained that adipose enlargement and adipocyte hypertrophy generate a hypoxic environment which trigger the secretion of proinflammatory adipokines which, in turn, may be further involved in the development of obesity and associated diseases (8).

The "ongoing story" of leptin (9) was described by: (i) Arieh Gertler (Rehovot, Israel) focusing on leptin receptor antagonists' anti-inflammatory and anti-fibrotic potentials in autoimmune diseases and liver cirrhosis, also cachexia in can-

cer and AIDS (10), (ii) Morris Karmazyn (London, Ontario, Canada) paving the molecular pathway of leptin-induced cardiomyocyte hypertrophy, demonstrating a significant activation of the RhoA/ROCK pathway and an increased polymerization of actin, showing that leptin receptor antagonists may improve heart function in experimental model of myocardial infarction (11), (iii) Jerzy Beltowski and Andrzej Marciniak (Lublin, Poland) presenting data of leptin's thrombogenic and atherogenic effect, revealing that leptin (a) increases thromboxane A₂ formation (12), and (b) inhibits paraoxonase I activity, thus enhancing protein homocysteinylation - these events are prevented by (a) the PPAR- γ agonist rosiglitazone, and (b) a synthetic liver X receptor agonist, and (iv) Esin Gurel (Ankara, Turkey) showing leptin-induced changes in erythrocyte rheology after oxidative stress.

Johan Renes (Maastricht, The Netherlands) highlighted the present adipoproteome map, revealing that proteomic technologies are fascinating tools for the identification of new adipokines and organelle-specific proteins (13).

Mariyana Hristova (Varna, Bulgaria) presented ongoing results about their hypothesis of metabotropic potentials of NGF and brain-derived neurotrophic factor (BDNF) as related to CMD (14), reporting effects of the anti-diabetic drug metformin and nonsteroid anti-inflammatory drugs on serum NGF and BDNF levels in patients with mild and with advanced stage of metabolic syndrome. Yu Nofuji (Fukuoka, Japan) presented findings showing that physical activity altered serum BDNF levels (15) as well as appreciated the recent data of BDNF as a myokine, that is, a cytokine secreted by skeletal muscles (16). Marcia Hiriart's (Mexico city, Mexico) pioneering data on NGF secretion by pancreatic beta cells (17) were extended in her SOS lecture on the involvement of peripancreatic adipose tissue in sucrose-induced metabolic syndrome in rats. Marco Fiore and Mauro Ceccanti (Rome, Italy) demonstrated that chronic prenatal exposure of mice to ethanol, but not red wine, causes memory deficit expressed by reduced presence of brain NGF, BDNF and choline acetyltransferase reactivity in the offspring (18).

Dragan Djuric (Belgrade, Serbia) focused on the role of folic acid and homocysteine, which is also "secreted" by adipose tissue (19), in coronary artery functions evaluated by coronary flow and oxidative stress biomarkers. Bilge Pehlivanoglu (Ankara, Turkey) associated obesity with immune cell responses to stress. Hiroshi Yamamoto (Kanazawa, Japan) looked for the "enemies and friends within" the mechanisms of diabetic angiopathy. He portrayed the AGE-RAGE-

esRAGE system, that is, advanced glycation end-products and their receptors, and an endogenous secreted splice variant coding for a decoy form of RAGE, respectively (20). Neşe Tunçel (Eskişehir, Turkey) implicated white- and brown adipose tissue-derived nitric oxide and associated mast cells in cold stress-mediated vascular contractility in rats (21), referring also to the recent challenge in brown adipobiology (22).

Sukhinder Cheema (St. John's, Newfoundland, Canada) highlighted the paradigm of nutrition-related developmental programming as related to the prevention of CMD, showing that a maternal high-fat diet alters the lipid metabolism, including hepatic LDL receptor expression, of their adult male offspring (23). Vladmila Bojanić (Niš, Serbia) reviewed data showing the effects of placenta- and breast milk-derived leptin on mother's and offspring's health, the so-called leptin-mediated metabolic programming (see 10). Collectively, CMD prevention should start during *in utero* and suckling life of the human. Likewise, Harpal Buttar (Ottawa, Ontario, Canada) advocated that "prevention is better than cure". There is an overwhelming evidence that the Mediterranean-type diets which are high in fibre, low in saturated fat and glycemic load are associated with the decreased prevalence of metabolic syndrome and diabetes mellitus as well as improved lipid homeostasis and reduced risk of CMD. Of note, Harpal Buttar mentioned recent data of Yuji Matsuzawa's group demonstrating that smoking cessation is associated with increased plasma levels of adiponectin, an anti-atherogenic and anti-diabetic adipokine (24). Richelle McCullough (Winnipeg, Manitoba, Canada) presented findings demonstrating that flaxseed is an excellent source of alpha linolenic acid (ALA), which is stored in adipose tissue, and that dietary flaxseed inhibits cardiac arrhythmias and reduces atherosclerosis (25).

Gorana Rančić (Niš, Serbia) implicated adipose-pineal network in the chronobiology of CMD. Luigi Aloe and George Chaldakov raised a hypothesis of adipose tissue as a third brain (26) - this sophisticated tissue is a source of and target for a variety of hypothalamus-pituitary hormones, releasing factors, neuropeptides and neurotrophic factors, which play a pivotal role in lipid, glucose and energy homeostasis as well as learning, memory and other neural functions. This may open a novel field of research, neuroadipology, which may contribute to further study of the pathogenesis of CMD (26,27; for leptin's neurotrophic action, see 10).

As we started this Report, "the adipose tissue in the human body is there for the best, the bad and the worse". "The best",

because adipose tissue produces (i) anti-obesity, anti-inflammatory and anti-atherogenic factors such as adiponectin, brain-derived-neurotrophic factor (BDNF), interleukin-10, IL-1 receptor antagonist, (ii) vascular relaxants such as adipose-derived relaxing factors, nitric oxide (NO), hydrogen sulfide (H₂S), and adiponectin, and (iii) neurotrophic factors such as NGF, BDNF, ciliary neurotrophic factor, leptin, and NPY and other neuropeptides. “The bad”, because adipose tissue produces pro-inflammatory factors such as tumor necrosis factor- α and various cytokines and chemokines with such an activity. “The worse”, because adipose tissue when (i) disappear resulting in lipodystrophies, and (ii) accumulate around vital organs in the human body leading to various cardiometabolic diseases.

Altogether, adipose tissue may be a crossroad of CMD and neurodegenerative diseases. Further progress in adipobiology and adipopharmacology holds much promise for understanding how to walk on that road. Finally, all participants broadcasted the signal of “SOS for *Homo obesus*”, to hopefully reach politicians and businessmen, and make them altruistic to science and human health.

ACKNOWLEDGEMENTS

We appreciate the financial support provided by GlaxoSmith-Klein, Deta Maritime Ltd, Bulgarian Ministry of Education and Science, Novo Nordisk, Wörwag Pharma, Sanofi Aventis, Actavis Bulgaria, Berlin-Chemie/Menarini, Technostroi EOD, Sofia, Bulgaria, and the International Federation for Cell Biology as well as personal donations of Mr Georgi Georgiev (Varna, Bulgaria) and of our colleague-friends Ion David (Bucharest, Romania), Wale Sulaiman (New Orleans, LA, USA), Iliyan Ivanov (New York, NY, USA) and Denis Kamberov (Florida, USA). The creative reading of the manuscript by Gema Frühbeck (Pamplona, Spain) is sincerely appreciated.

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