OBESITY: AN INSIDE VERSUS AN OUTSIDE VIEW. JIMMY BELL AND THE LITTLE PRINCE A SCIENCE-IN-FICTION DEDICATED TO WORLD OBESITY DAY 2017

George N Chaldakov

Department of Anatomy and Cell Biology, Faculty of Medicine, Medical University of Varna

ABSTRACT

Since 2015 the World Obesity Foundation has been organizing the World Obesity Day on October 11. The motto of the World Obesity Day 2017 was: „We need to treat obesity now to avoid its consequences later". Accordingly, one of the appeals of the World Obesity Foundation proclaimed: "We are calling on all governments, health service providers, insurers and philanthropic organisations to prioritise investment in tackling obesity. This means investing in obesity treatment services, early intervention and prevention."

Keywords: *obesity, adipobiology, obesity complications*

Obesity is Globesity *Today*

Among the noncommunicable diseases (NCD), obesity is most prevalent human health disorder globally and, consequently, the term *globesity* has emerged recently. Obesity is a major risk factor for a large number of NCDs such as cardiometabolic diseases (atherosclerosis, hypertension, type 2 diabetes, metabolic syndrome). According to the World Health Organization (WHO) these diseases account for most NCD deaths - 17.7 million people annually, followed by cancers (8.8 million) and respiratory diseases (3.9 million). Altogether, these diseases account for over 80% of all premature NCD deaths. Further, WHO's key facts updated in October 2017 demonstrated the following: (i) worldwide obesity has nearly tripled since 1975, (ii) in 2016, more than 1.9 billion adults were overweight (BMI 25.0 - 29.9 kg/m^2); of these over 650 million were obese (BMI over 30 kg/m^2), (iii) 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese, (iv) 41 million children under the age of 5 were overweight or obese in 2016, (v) over 340 million children and adolescents aged 5-19 were overweight or obese in 2016, and (vi) it is predicted that overweight and obese people may be 2.7 billion in 2025.

Obesity and Adipose Tissue

At its core, obesity may be briefly classified as accumulation and inflammation of white adipose tissue (1,2) and dysfunction of brown adipose tissue (3). Arguably, basic and translational studies on cardiometabolic diseases are associated with the "rediscovery" of a neglected tissue, the adipose tissue (4-9). It was recognized as a vital player not only in the "classical" control of lipid and energy balance, but also of inflammation, immunity, reproduction as well as cardiovascular and neuronal homeostasis. Adipose tissue is a cellular and extracellular matrix assembly composed of adipocytes, fibroblasts, immune cells and matrix components, also rich in sympathetic nerve fibers, blood vessels, and stem cells.

Address for correspondence:
George N Chaldakov
Department of Anatomy and Cell Biology,
Medical University of Varna,
55 Marin Drinov St,
9002 Varna, Bulgaria
e-mail: chaldakov@yahoo.com

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There are two major subtypes of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). In human body, WAT is the major endocrine and paracrine system secreting more than 600 signaling proteins collectively termed *adipokines* (4-7), whereas BAT increases the energy expenditure realized by uncoupling respiration from ATP synthesis via uncoupling protein 1 (UCP1) expressed in the inner mitochondrial membrane of brown adipocytes, thus mediating a process known as thermogenesis (3). Noteworthy, animal studies have shown that the activation of BAT counteracts diet-induced weight gain and related disorders such as type 2 diabetes and metabolic syndrome; it may also be the case for humans. Recently, the knowledge of WAT and BAT has been enriched with their derivatives, namely brite (brown in white) adipocytes and brucle (brown in skeletal muscle) adipocytes. The stimulation of BAT can potentially increase total daily energy expenditure and is seen as a possible target to prevention, diagnosis or therapy of obesity and its related diseases, whereas whitening of BAT may stimulate the development of atherosclerosis and metabolic syndrome (3). Cumulatively, the studies on the structure and function of adipose tissue in health and disease were conceptualized as *adipobiology* (4).

White adipose tissue is located in two large-scale depots, subcutaneously and abdominally, which are well-visible, and multiple small depots (Fig. 1) (4), which are invisible without using some imaging technologies, such as echography, magnetic resonance imaging (MRI) and computer tomography (CT). Small adipose depots are located around the heart, blood vessels, pancreas, ovaries, prostate gland, and lymph nodes. These organs are subjected to the action of pro- and anti-inflammatory adipokines, the disbalance of their secretion being involved in the development of cardiometabolic diseases, polycystic ovarian syndrome, prostate and breast cancer (Fig. 2) (6-9), also Alzheimer's disease.

Paradigm Shifts in the Adipobiology of Obesity

In the second half of the 20th century, holism (from the Ancient Greek word *holos,* meaning whole, entire) led to thinking in terms of systems and their derivatives, such as *systems biology* – an interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach instead of the more traditional reductionism to biological research.

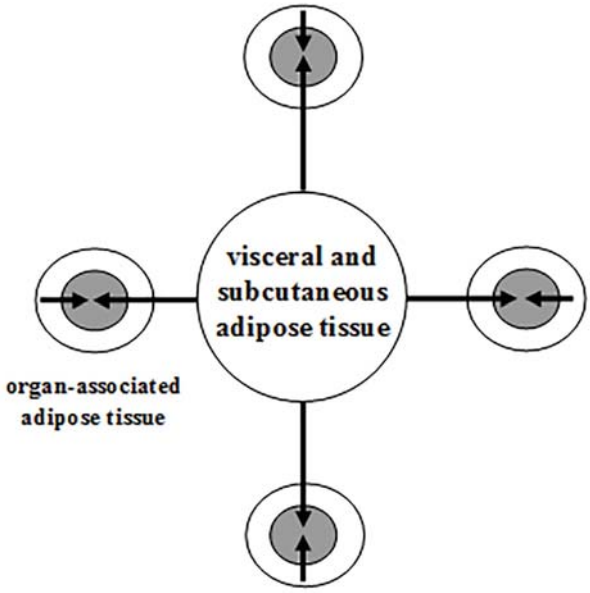

Fig. 1. Schematic illustration of a large adipose depot (visceral and subcutaneous adipose tissue) and small adipose depots (organ-associated adipose tissue). Endocrine action (long arrows) and paracrine action (short arrows) of adipokines and of other adipose-derived signals on various organs. Organ parenchyma (grey) is surrounded by adipose tissue (white). (From: Chaldakov GN, Stankulov IS, Hristova M, Ghenev PI. Adipobiology of disease: adipokines and adipokine-targeted pharmacology. Curr Pharm Des. 2003; 9(12):1023-31)

In 1962 Thomas S. Kuhn published his book The Structure of Scientific Revolutions (1st edition, University of Chicago Press, Chicago, USA). Its publication was a landmark event in history and philosophy of scientific knowledge (epistemology). Kuhn challenged the then prevailing view of "normal science" which was viewed as "development-by-accumulation" of accepted facts and concepts often leading to epistemological paralysis, we dubbed it *neophobia*. Kuhn suggested a model in which a period of such conceptual continuity in normal science was interrupted by a period of revolutionary science leading to a new paradigm, an event he designated as *paradigm shift*. At an epistemological level, the adipose tissue has undergone several paradigm shifts in the last 20-25 years. This raised it above the horizon to take center stage in so many diseases that it leaves most scientists and medical doctors astonished.

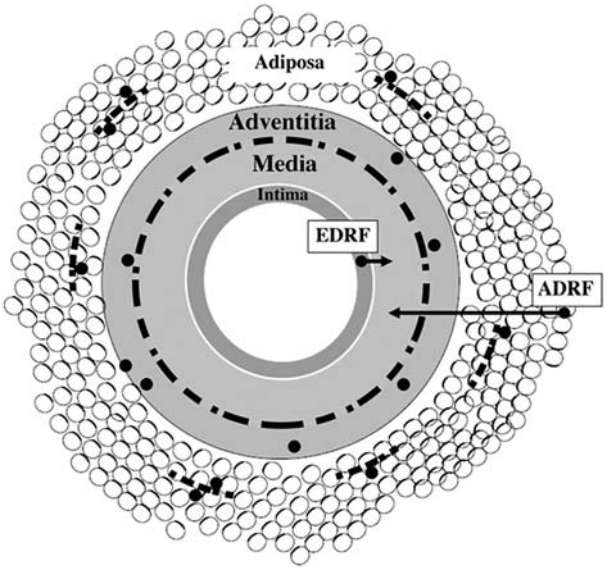

Fig. 2. Schematic presentation of a vascular wall composed of four tissue coats (tunicae): intima, media, adventitia, and adiposa. Arrows show that tunica media is a target for at least two vasorelaxing factors, endothelium-derived relaxing factor (EDRF) and adipocyte-derived relaxing factor (ADRF), respectively. Dashed black line positioned at the adventitia–media border illustrates the perivascular nerves. Small-sized dashed black lines located in tunica adiposa indicate adipose nerves. Black granules (except those linked to arrows) illustrate immune cells – their association with nerves and adipocytes is also depicted. (From: Chaldakov GN, Fiore M, Ghenev PI, Beltowski J, Rancic G, Tunçel N, et al. Triactome: neuro–immune–adipose interactions. Implication in vascular biology. Front Immunol. 2014;5:130).

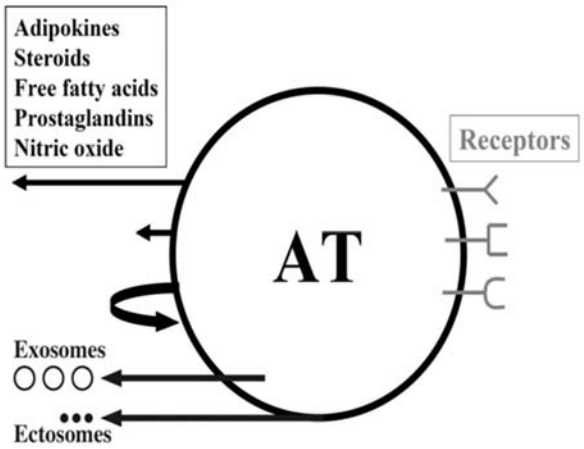

Fig. 3. A drawing illustrating both the secretory and receptor nature of adipose tissue (AT) cells. At the secretory level, AT-derived signaling molecules communicate via multiple pathways, such as endocrine (arrows 1, 4 and 5, from top to bottom), paracrine (arrow 2) and autocrine (arrow 3, curved). Also depicted is that AT cells express receptors for various ligands. (From: Chaldakov GN, Tuncel N, Beltowski J, Fiore M, Rančić G, Tonchev AB, et al. Adipoparacrinology: an emerging field in biomedical research. Balkan Med J. 2012; 29:2-9).

The first paradigm shift in adipobiology states that while considered a passive storage-release of lipids by most cell biologists and pathologists for a long period of time, adipose tissue is now viewed as the biggest endocrine and paracrine organ of the human body (Table 1, Fig. 3) (9).

Table 1. A paradigm shift: never before has adipose tissue been so active

FROM
Adipose tissue is a lipid and energy storage involved in obesity
TO
Adipose tissue is an endocrine and paracrine organ
Produces neurotrophic factors, neuropeptides, neurohormones
Produces steroid hormones
Adipose tissue is an immune organ
Adipose tissue is a source of and target for inflammatory mediators
Adipose tissue produces all components of rennin-angiotensin system
Adipose tissue produces and processes amyloid precursor protein (APP)
Adipose tissue is thus involved in numerous diseases beyond obesity

The "heroes" in the present science-in-fiction are:

(i) Jimmy Bell - Professor of Imaging and Molecular Medicine at the Center for Clinical Sciences, Hammersmith Hospital, Medical Faculty of the Imperial College in London, UK,

(i) the Little Prince - the most charming hero of the famous Antoine de Saint-Exupery, and

(iii) TOFI, TOTI, FOFI and FOTI.

- Good day - Jimmy Bell said.

- Good day - the Little Prince said.

- Good day - responded in choir TOFI, TOTI, FOFI and FOTI.

JB: Being lean does not mean you are not obese. The second paradigm shift in adipobiology of obesity derived from our study of scanned 477 white volunteers with MRI technique, aimed at obtaining an internal map of WAT (10). In support of TOFI (thin outside, fat inside) subphenotype, we have demonstrated that as many as 45 percent of women and nearly 60 percent of men scanned have normal scores of the body mass index (BMI, 20–25 kg/m^2). These people were thin outside (TO), while actually having excessive levels of internal adipose tissue – they are fat inside (FI), hence a TOFI phenotype of obesity. Noteworthy, TOFI was also found among people who were professional models. In brief, TOFI may be considered an "invisible" expression of *Homo obesus.*

LP: The essential is invisible to the eyes. To remember it, the Little Prince repeated: The essential is invisible to the eyes.

JB: Yes, TOFI is a Trojan horse in the human body, including elegant women - some models are also TOFI because they keep low-calorie diets but do not exercise.

LP: What should a man do with his or her adipose tissue to have normal metabolism and blood vessels?

JB: The adipose tissue is the human's body largest gland with internal secretion - it produces multiple signaling proteins, collectively termed *adipokines* (4-7).

LP: What should a man do with his or her adipose tissue to have normal metabolism and blood vessels? Asked the Little Prince again, when JB had not answered his question.

JB: Eat low-calorie food, more fruits and vegetables, less salt - to be thin outside. To exercise every day, about 30 minutes of light running or fast walking - to be thin inside – in effect, that is TOTI, a healthy phenotype.

LP: And they will see how everything changes. And no politician will ever understand how important it is, because the hearts of these people are obese.

Then TOFI, TOTI, FOFI and FOTI gave their business cards (Table 2) to ministers and other politicians and showed them the financial costs of treating obesity-associated illnesses (Fig. 4). Thus reminding them that "we are calling on the *Bulgarian government*, health service providers, insurers and philanthropic organisations to prioritise investment in tackling obesity. This means investing in obesity treatment services, early intervention and prevention."

Table 2. Adipotopography (fat mapping): variations+

TOFI**	thin outside, fat inside
TOTI*****	thin outside, thin inside
FOFI*	fat outside, fat inside
FOTI**	fat outside, thin inside

+The number of asterisks indicates the quality of cardiometabolic health, as related to adipose tissue distribution. Thus, TOTI represents the highest quality and FOFI - the lowest quality of cardiometabolic health. Therefore, be a TOTI. (From: Rancic G, Petrovic A, Sekulovic-Stefanovic L, Bojanic V, Ghenev PI. Adipotopography: TOFI versus TOTI, or a hidden Homo obesus [abstract]. The First International Symposim on Adipobiology and Adipopharmacology, 20 October 2007, Varna, Bulgaria. pp 13-14).

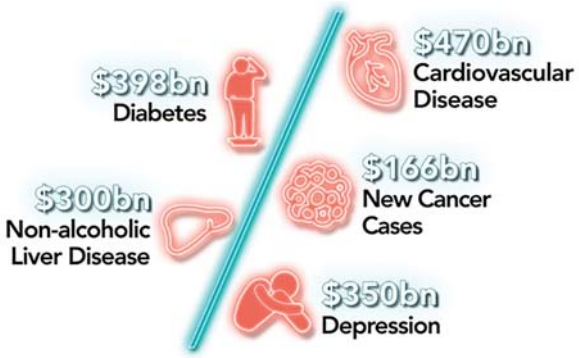

Fig. 4. US Dollars in billions (bn-billion) used globally in 2014 to treat diseases related to obesity. (From: www.worldobesity.org).

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Conflict of Interest

The authors declare no conflict of interest

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