Focus on the fire of life
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Abbreviations
NEAT  non-exercise activity thermogenesis
TDEE  total daily energy expenditure

Introduction
In 1961 Max Kleiber published the book The Fire of Life [1]. It is still one of the classics in the field of animal and human bioenergetics. In his book he focussed on the parallel between animal and human life and fire, emphasizing the generalizations of biophysics rather than the differentiations of biochemistry. Life involves much more than chemical potential, work and heat. Modern nutrition is concerned with more than the supply of energy, yet energy transfer remains one of the basics in physiology in general and of nutrition in particular. Especially nowadays, with the unravelling of the human genome providing the first glimpse of candidate genes in bioenergetics, it becomes more and more clear that the concluding remark from Charles Darwin's book The Origin of Species really points to the fire of life: 'The evolution of higher animals directly follows...from the war of nature, from famine and death...' [2].

In the last century nutritional sciences research has been devoted for a large part on the effects of malnutrition since this was the greatest challenge related to health and disease in the world. It looks as though, for the coming decades and maybe the whole century, overfeeding will dominate the nutritional research agenda observing the morbidity and mortality statistics in the world. Again it all has to do with the bioenergetics and the consequences for the quality of life.

Thrifty genes and the observed variation in bioenergetics
In 1960 Neel postulated for the first time the so-called thrifty gene theory based on his research in diabetes [3]. The selection period that has covered almost 100% of human life on earth has been dominated by periods of feast and famine, which has facilitated the ability to lay down extra adipose tissue and this survival trait from ancient times has become a treat instead of a redundancy trait in the modern world. Especially, those who could build up large quantities of adipose tissue in periods of feasting and gorging were the ones who survived long periods of famine. Darwin had already observed this most pervasive selection force of species.

Therefore information about the variation in bioenergetics is of importance to understand better the origin of a number of today's chronic diseases, such as diabetes, obesity and cardiovascular disease.

In the feed industry it has already been known for a long time that there are large differences in energy efficiency between animals within species [4]. But even in humans we now have solid data that there is large variation in the handling of excess energy intake [5,6]. The classical overfeeding study in identical twins from Bouchard et al. clearly showed a threefold difference in the ability to lay down excess calories in weight [5]. Based on a more detailed description by Tremblay et al., the energy efficiency was calculated to range from 33 to about 100% in these 12 identical twins (Table 1) [7]. Also in the shorter, overfeeding study of Levine et al. [6] with young men, a similar variation in energy efficiency was found.

Considering that the selection process has taken place over many millions of generations it is remarkable that the differences have their origins in the genetic variations (single nucleotide polymorphisms) in particular genes, or maybe in thousands of genes. The unravelling of the mystery of the fire of life is at full speed now with all the high throughput genomic capacity. Nevertheless, at the same time we need to update our physiological information in order to link the genetic and molecular know-how to the genotypic function.

The variation in minimal and maximal metabolism
In order to make comparisons between the energy metabolism of individuals within or between species, the conditions under which the measurements are based must be standardized. This is achieved by attempting to measure a minimum rate of energy expenditure free of effects of any controllable factors known to increase it.
Such factors include muscular exercise, the consumption of food and its subsequent metabolism and the physical environment. The object of standardization is to ensure comparability of estimates rather than to establish some absolute minimum value of metabolism [4].

In many situations it is impractical to fast or feed humans under a strictly controlled way as defined for measuring basal metabolic rate, yet some standardized estimate of metabolism is required. Metabolism determined without the criteria applied for the fasting or feeding state, but with the remaining conditions listed by Benedict being met, is termed the resting metabolic rate.

This is one of the primary components in the factors contributing to the variation in total daily energy expenditure (TDEE) reviewed in the paper in this issue by Donahoo, Levine and Melanson. They conclude that the coefficient of variation of all components of TDEE is rather reproducible. TDEE varies many-fold in humans, not due to variation in resting metabolic rate, diet induced thermogenesis or exercise thermogenesis, but due to variations in non-exercise activity thermogenesis (NEAT). A variety of factors impact NEAT of which, most probably, genetic factors including sex are dominant. In the light of the emerging obesity epidemic, further elucidation of the potential candidate genes and their variations is needed. So far, from the genetic and molecular level, it can more or less be considered as a black box. Recently Ukkola and Bouchard [8] reviewed the findings of an analysis of a panel of candidate genes to explain the variation in response of the twin overfeeding study. Among the most significant findings, an adipsin polymorphism was associated with the increases in body weight, total fat mass and subcutaneous fat. In addition the beta-2 adrenergic receptor gene Gln27Glu polymorphism showed a strong association with the gains in body weight and subcutaneous fat. The changes in the insulin parameters brought about by the long-term overfeeding were influenced most consistently by the leptin receptor (LEPR) Gln223Arg gene variant. Further research with larger sample sizes should make it possible to identify the specific contribution of DNA sequence variations to the individual response in energy efficiency.

Changing the focus on the maximum of human metabolism Westerterp and Plasqui describe in their contribution to this issue the upper limits of human energy expenditure. Based on the large cross-sectional database on measurements using the very valid doubly labelled water method; they conclude that in the normal population the upper limit of the physical activity index (equal to total energy expenditure as a multiple of resting metabolic rate) is about 2.5. However in a large part of the population the level is only around 1.6. The best current estimates are that the physical activity of ancestral humans averaged about 1000 kcal per day and that their caloric need was about 3000 kcal per day, representing today’s demonstrated upper limit of the physical activity index of around 2.3 [9]. This indicates that we have a long way to go before our modern physical activity habits fit within the metabolic capacities of our gene pool selected at that ancient time.

Metabolic consequences of a high or low fire of life

In the 1930s it had already become clear that caloric restriction has effects on retarding the effects of ageing and extending life. Lowering your fire will effect your life. In this section, Smith, Heilbronn and Ravussin review the existing knowledge on the link between calorie restriction and ageing. An overwhelming number of studies have shown that calorie restriction extends both the median and maximal lifespan in a variety of lower species such as yeast, worms, fruit flies, fish, rats and mice.

The mechanisms of this lifespan extension via calorie restriction are not yet fully elucidated, but possibly involve significant alterations in energy metabolism, oxidative damage, the sympathetic nervous system and in particular insulin/insulin-like growth factor signalling. In particular the new genomics technology of microarray gene expression have brought much light onto the basic mechanisms of how a lower fire is linked to life, and particular extension of life. New genes such as DAF16, never linked before with the energy metabolic routes, have turned out to be of crucial importance. However Smith and co-authors conclude that only controlled human trials involving long-term caloric restriction can ultimately link observed alterations from body weight and composition down to changes in molecular pathways and gene expression, with their possible effects on the biomarkers of ageing.

How much overfeeding restricts life is becoming a hot topic in nutritional research. Tappy describes in his review the metabolic consequences of this currently so

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<th>Table 1. Effects of 100 days' overfeeding with 1000 kcals per day on weight gain and energy efficiency defined as percentage of body energy gain versus excess energy intake</th>
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<td>Mean</td>
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<td>Body weight gain (kg)</td>
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<td>Fat gain (kg)</td>
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<td>Energy efficiency (%)*</td>
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*Body energy gain was derived from densitometric measurements assuming that the energy equivalent of fat was 38.9 MJ/kg and that of fat free mass was 4.3 MJ/kg. Data from Bouchard et al. [5] and Levine et al. [6].
It is of interest to finish this editorial comment with a quote from the preface of the book by Kleiber. He described classical aspects of the animal energetics in his book as going ‘out at a time when much of what is new today will be out by tomorrow. Some of the old knowledge, however, should not be forgotten.’ We still can learn from this old knowledge about the fire of life.

References