Energy, evolution, and human diseases: an overview1–4

Jesse Roth, Alessandra L Szulc, and Ann Danoff

ABSTRACT
In the symposium entitled “Transcriptional controls of energy sensing,” the authors presented recent advances on 1) AMP kinase, an intracellular energy sensor; 2) PGC-1α (peroxisome proliferator-activated receptor γ co-activator 1z), a transcriptional co-activator that has powerful effects on mitochondria; 3) methylation and demethylation in response to metabolic fluctuations; and 4) FGF21 (fibroblast growth factor 21) as an emerging hormone-like intercellular metabolic coordinator. This introduction places these advances within a broad overview of energy sensing and energy balance, with a focus on human evolution and disease. Four key elements of human biology are analyzed: 1) elevated body temperature; 2) complex prolonged reproductive pathways; 3) emergence of 4 large, well-defined fat depots, each with its own functional role; and 4) an immune system that is often up-regulated by nutrition-related signals, independent of the actual presence of a pathogen. We propose that an overactive immune system, including the “metabolic syndrome,” was adopted evolutionarily in the distant past to help hold out against unconquerable infections such as tuberculosis, malaria, and trypanosomiasis. This immune activation is advantageous in the absence of other disease management methods, especially under conditions in which life expectancy is short. The inflammation has become a major agent of pathology in wealthy populations in whom the pathogens are a minor threat and life expectancy is long. The “Conclusions” section sketches cautiously how understanding the molecules involved in energy sensing and energy balance may lead to specific therapies for obesity and diabetes and for their complications.  

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ENERGY SENSING AND ENERGY BALANCE
This symposium, entitled “Transcriptional controls of energy sensing,” brings together experts on the rapid advances that are being made in understanding how energy needs of the body are sensed, registered, and fulfilled. This overview will link the recognition of energy needs to energy balance in each cell and in the whole body. A surprisingly large number of close links and important overlaps between energy-related processes and the body’s immune defense system have been recognized recently. The effects are especially prominent in people who are overweight. Consideration of the evolutionary forces that may have driven the intertwining of the 2 systems (energy balance and antimicrobial defenses) will encourage a broader appreciation of the studies presented by our 4 invited experts. Applications to metabolic disease states and potential therapies conclude this overview.

1 From the Feinstein Institute for Medical Research, Elmezzi Graduate School of Molecular Medicine, North Shore-Long Island Jewish Health System, Manhasset, NY (JR and ALS); Hofstra North Shore-LIJ School of Medicine, Hempstead, NY (JR); Albert Einstein College of Medicine, Yeshiva University, Bronx, NY (JR); the Division of Endocrinology, Diabetes, and Metabolism, New York University Medical Center, New York, NY (AD): and the VA New York Harbor Healthcare System, New York, NY (AD).
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4 Address correspondence to J Roth, 149-37 Powells Cove Boulevard, Whitestone NY 11357. E-mail: jesserothmd@hotmail.com.
AMP-activated protein kinase

In his article, Hardie (2) introduces AMP-activated protein kinase (AMPK) as a major energy sensor in cells throughout the body. It is activated when the AMP/ATP ratio in the cell rises—i.e., because ATP production slackens, ATP consumption is accelerated, or both. In this way, AMPK also acts to sense glucose deprivation and, in a grander way, impending starvation at the cellular level. It activates catabolic (ATP-generating) pathways and impedes ATP-consuming processes. Hardie reminds us that the mitochondria are heavily influenced by AMPK and that AMPK is the site of action of metformin, one of the most widely used antidiabetes agents, and of resveratrol, an ingredient of red wine that is one of the most highly touted natural agents.

PGC-1α

The name of PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α, is derived from the name of its mate, PPAR-γ (peroxisome proliferator-activated receptor-γ). As Fernandez-Marcos and Auwerx note in their article (3), PGC-1α is a master regulator of the biogenesis of mitochondria and a key player in energy expenditure. PGC-1α regulates the activity of its name mate, PPAR-γ, and an array of other transcription factors including PPAR-α, FoxO1, HNF4α (hepatic nuclear factor 4α), ERRα (estrogen receptor-related α), and NRF1 (nuclear respiratory factor 1). By regulating the activity of such proteins at the transcriptional level, PGC-1α modulates the activity of many genes whose protein products are involved directly in metabolic pathways that carry out gluconeogenesis, fatty acid synthesis, glycolysis, and oxidation. Energy regulation for both thermogenesis in brown fat and exercise in muscle involve PGC-1α. As noted above, a threat to the energy supply prompts AMPK to stimulate many catabolic pathways, including activation of mitochondria, a process in which PGC-1α plays a central role. One should recall that the glitazones, antidiabetes drugs in wide use, are PPAR activators.

DNA methylation

Each differentiated cell at any moment expresses only a small fraction of its genes. Differences in gene expression give each cell its characteristic behavior. Barres and Zierath (4) point out that methylation of cytosines in DNA is a widely ongoing occurrence throughout the genome; methylation impedes that gene’s expression by altering access for the transcription machinery. They describe how nutrients, hormones, and other agents can alter DNA methylation (and demethylation) profiles and recruitment of the transcription machinery to promoters of genes involved in the metabolic functions of skeletal muscle and adipose tissue (as well as other tissues that are at center stage in metabolic disorders).

Fibroblast growth factor 21

As described by Domouzoglou and Maratos-Flier (5), fibroblast growth factor 21 (FGF21) is an emerging member of a 22-member superfamily of proteins that have structural similarities to FGF; the pater familias. FGFs regulate growth, development, and a host of other functions including metabolism. FGF21 and several other members of the family are categorized as hormone-like FGFs: they lack a heparin sulfate binding domain, are released into the circulation, and require a co-receptor for binding and receptor activation. FGF21 is produced predominantly in the liver and fat. FGF21 expression in liver is increased 20-fold with fasting; refeeding produces a swift fall. FGF21 has a multiplicity of actions on metabolism, both in the fed and fasted state; its physiologic actions are prominent during fasting when it acts to regulate fatty acid oxidation and ketone formation. The transcription factor PPAR-α is a critical (but probably not sole) regulator of FGF21.

INTEGRATION

The mechanisms developed to meet each individual cell’s energy needs must be integrated with the broader needs of specific tissues, organs, and organ systems that constitute the whole organism. To fully use the critical advances in our understanding of intracellular processes that are being expounded by each invited expert, we present an overview of the overall biology, including evolutionary pressures, physiology, pathophysiology, and disease mechanisms, especially obesity and its complications.

TASK AT HAND

Balancing the day-to-day energy needs of one cell goes back to the beginning of life 3.5 billion years ago. Mitochondria, key participants in the energy equation at the cellular level, show up with unicellular eukaryotes a little over 1 billion years ago. Balancing the overall needs of a multicellular organism began approximately 0.8 billion years ago. The very complex needs of specialized tissues (eg, muscle, nerve) are newer yet, as are the complexities of organs (eg, brain and kidney). The mechanisms used at each new level are derived from and superimposed on the earlier solutions.

A recurrent (but at this time unanswered) question will be, which group of cells at which site are sensing the greater needs of an organ or of a whole organism? Which cells decide how much we take in when? Which decide how the energy budget will be partitioned and expended, now and under altered circumstances? Where and how is the total amount of stored energy being assessed? How is that assessment shared with other sites? At the next level, what molecules are being called into play to participate in these delicate life-determining decisions? The specific answers lie well into the future, but the invited experts in this symposium give us a hint of where the field is headed.

EVOLUTION AFFECTS ENERGY BALANCE IN MAMMALS

Mammals and birds emerged 100–200 million years ago, roughly equivalent to the latest 5% of the timeline of life on this planet. Humans and their nearest relatives are newcomers, arising in the mammalian line in the past 0.1–0.2 million years. With an eye to the pandemic of obesity and diabetes worldwide, we have chosen to review 4 of the elements that have strong influences on energy sensing and energy balance in humans: 1) body temperature, 2) reproduction, 3) highly organized fat deposits, and 4) the immune system with its defenses against infectious agents.

BODY TEMPERATURE

Both birds and mammals adopted a high fixed body temperature, which carries an extraordinary energy demand (6). It also
makes them vulnerable to swift death by hyperthermia and hypo-thermia under environmental conditions that might well spare their poikilothermic cousins. This narrow range of temperatures compatible with life constrains multiple aspects of energy expenditure management. Note one additional new threat to life: the switch to a fixed high body temperature likely changed quite substantially the roster of infectious diseases that afflict birds and mammals (6).

HUMAN REPRODUCTION

Compared with most other living beings, reproduction in humans is unusually costly in energy and in raw materials. Approximately 6,000,000 calories are needed to produce one fertile 12-year-old ready to become pregnant. She will produce only one offspring at a time, only about once every year or 2. Recall that puberty, menses, and fertility are highly dependent on a minimum body mass—ie, stored calories (7). Even including that trousseau, when embarking on the pregnancy, the new mother-to-be has in her body only a fraction of the mass of raw materials that she will need (acquired in a precisely timed way) to bring the infant to term successfully and to ensure her own survival and that of the baby postnatally. (Most miraculous is the total shift in but a few days from mother with fetus in utero to an infant supported by the newly developed mammary gland.) Clearly, reproduction as we know it succeeds only because of the extraordinary ability of the mother and infant to manage a series of shifts in energy input and expenditure.

FAT DEPOSITS

Fat in large discrete deposits first emerged with birds and mammals (8), which gives them a big advantage in managing wide fluctuations in energy supply and demand. In addition to efficient storage of calories, fat depots also prevent hypothermia by acting as insulation (energy saver) and as heat generators (energy dissipators). Fat tissue is also an endocrine gland, releasing leptin (proinflammatory) and adiponectin (antiinflammatory), 2 hormones that affect energy intake and utilization as well as immunity. Fat also secretes a score of other hormone-like agents and other molecules. With increasing fat mass (which occurs in the face of a seemingly trivial excess of calories consumed over calories burned), there is an increase in the production of proinflammatory molecules [eg, TNF (tumor necrosis factor) and IL-6 (interleukin-6)]. This is augmented by macrophages recruited to the fat depots, where they are activated and release additional proinflammatory molecules (9–16). This important program is one that combats pathogens (described in more detail below) but simultaneously causes collateral damage to normal tissue (15–17).

Fat in some depots promotes inflammation more than does fat in other sites (Figure 1). Highly inflammatory fat depots are especially prominent around the waist. Indeed, the waist circumference measured with a tape measure gives size estimates of this fat depot that closely reproduces the measurement achieved with sophisticated scanning techniques. These deposits are commonly referred to as visceral fat, although peri-visceral or mesenteric would be more accurate. As these so-called visceral fat depots increase, fat is also deposited in other sites, including liver, heart, skeletal muscle, and β cells of the pancreas. These sites (which truly are “visceral” in location) are currently referred to as ectopic fat or metastatic fat by the scientific community. These ectopic fat depots also add to the proinflammatory mix, impairing function and in the longer term destroying the anatomy. Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), leading precursors of cirrhosis and liver failure, are the best studied of these pathologic processes.

Subcutaneous fat is the label used to describe traditional fat depots that are relatively low in inflammatory elements. Classic

![Adiposity (Body Mass Index)](https://academic.oup.com/jnci/article-abstract/93/4/875S/4597797/05 March 2019)

**Figure 1.** The link between body weight and inflammation. The curved line is a schematic representation of the baseline relation between inflammatory processes (largely derived from visceral and ectopic fat) and body weight in one hypothetical individual. This relation depends on a myriad of genetic and environmental elements including large influences of chronologic age and ethnic background. The down-directed arrow at the left heads a list of antiinflammatory influences. The up-directed arrow at the right heads a comparable list of in vivo elements that generate increases in proinflammatory influences.
examples of subcutaneous fat are the fat depots that define the sexually mature female and the limbs of young infants. Subcutaneous fat is more energy efficient, wasting fewer calories on inflammation-related processes.

**Brown fat**, the fourth type of fat depot in our discussion, is also low in inflammation. Well studied in rodents for decades, it has only recently been characterized in humans (18–21). Its major function is heat generation to prevent hypothermia, especially in young infants and in adults exposed to cold.

The fat deposits in these 4 fat compartments turn over rapidly, allowing swift realignment of the fat compartments. Changes in food intake, exercise, ambient temperature, pregnancy, Illness, or medications (eg. glucocorticoids and antiretrovirals) can cause large changes. Diabetes and most other serious diseases associated with obesity (including myocardial infarction, stroke, and dementia) are promoted by the deposition of excess fat into proinflammatory sites.

Identification and characterization of the molecules responsible for determining the deposition sites of the calorie excess will facilitate development of therapeutic agents that direct surplus calories into metabolically preferred (low inflammation) depots. This shift in fat depots, even without change in weight, would be expected to improve outcomes of many diseases associated with obesity. Activation of AMPK, activation of PGC-1α, and elevation of PGE21 levels (3 leading topics of this symposium) all potentially can have beneficial effects in this regard.

### EVOLUTION OF THE IMMUNE SYSTEM

Our type of **adaptive immunity** appears evolutionarily with the sharks along with "a considerable variety of cytokines and chemokines, adhesion molecules, co-stimulatory molecules and well defined primary and secondary lymphoid tissue . . . . This system was superimposed onto an innate system inherited from invertebrates . . . . Because of the perpetual conflict with pathogens, the immune system is in constant flux . . . . Rapid evolution of immune system molecules and mechanisms is a general rule" (22, 23; p 57 in reference 23). Compared with other systems of the body, the immune system is capable of unusually swift substantial changes, using existing elements in new ways (22, 23).

### ORGANIZATION OF THE IMMUNE SYSTEM

The immune system is remarkably effective (24–28). Of the truly countless millions on millions of species of unicellular and multicellular organisms in the universe, fewer than 1000 are capable of causing diseases in humans. (In addition, the intact immune system is an effective tumor suppressor.) Highlighting the effectiveness as a defense against infectious agents (and tumors) are patients who are immunocompromised—by AIDS, genetic forms of severe combined immunodeficiency disease, radiation, or chemotherapy—and who are very susceptible to multiple agents that are otherwise nonpathogenic (and to a variety of tumors) (22, 25).

### ADAPTIVE IMMUNITY

When most people think of immunity, they picture the adaptive immune system, which, after a lag of several days, forms highly specific antimicrobial responses that enable the host to rid itself of that specific pathogen. It is also the basis of immunizations.

### INNATE IMMUNITY

Evolutionarily much older and acting at every moment against all foreign entities is the innate immune system. Composed of hundreds of elements—cells, enzymes, messenger molecules, receptors, and highly reactive small molecules—it is continuously on guard, detecting and destroying every potential invader (22).

### OVERCOMING PATHOGENS

An organism that gets past the innate system’s first line of defense is attacked by mounting elements of the innate system; the latter also triggers the activation of the adaptive system. Within a few days, cells and molecules of the adaptive system, tailored to that specific invader, join with elements of the innate system to fight the microorganism. In a minority of cases, the invasion of the microorganism leads to death of the host. In most cases, the innate and adaptive systems, acting together, rid the host of all of the invaders. In addition, in most cases, the adaptive system elements provide near-permanent immunity from reinfection, which is limited to just that organism. The innate system elements lack such memory. These defense elements, in addition to destroying the invader, can cause collateral damage to host cells. Many degenerative diseases of middle and late life are negatively and inadvertently affected by elements of the host’s immune system (15–17). Indeed, inflammatory processes promote the emergence of diabetes. At the same time, diabetes impairs the function of both the innate and acquired immune elements in their struggle against invading pathogens.

### THE UNCONQUERABLES

With a small fraction of infectious invaders, the outcome is a precarious standoff (29). The host survives and the infectious agent persists. Some agents persist in a latent form, rarely causing serious trouble. With others, a continuing struggle ensues (see Table 1); the immune system remains activated, fighting the invader but unable to destroy it. The collateral damage continues as well (29).

### FAT AS AUXILIARY INNATE IMMUNE SYSTEM

When mammals evolutionarily added new organs in the form of fat depots, immune functions were included in the 3 largest (visceral, ectopic, and subcutaneous), linking immunity to calorie balance. The 2 main hormones of adipocytes, both newly evolved with the fat depots, each have immune- and food-related metabolic effects. With suboptimal nutrition, circulating concentrations of leptin are low and adiponectin is high; the immune system persists. Some agents persist in a latent form, rarely causing serious trouble. With others, a continuing struggle ensues (see Table 1); the immune system remains activated, fighting the invader but unable to destroy it. The collateral damage continues as well (29).
INTERACTIONS BETWEEN FOOD, REPRODUCTION, AND IMMUNITY

It had long been recognized that immunity and reproductive capacity are each impaired by poor nutrition. The very obese ob/ob genetically leptin deficient mouse sheds new light. These mice, despite massive energy stores, behave as if they are on the verge of starvation. In contrast to normal mice, which eat only at night, the ob/ob mice eat throughout the 24 hours. They maintain a reduced body temperature and sit motionless, which are energy-conserving maneuvers of starving animals. They are also infertile and immune deficient such as mice that are severely deprived of nutrition. Leptin-deficient humans share many similarities. Leptin replacement restores these missing functions in both mice and humans (33, 34).

Toll-like receptor 4 (TLR4), the classic immune system receptor for the endotoxin of gram-negative bacteria, is now known to bind and be activated by saturated fatty acids, which are surrogates of a rich diet (40). Animals lacking TLR4 are resistant to diet-induced dysregulation of metabolism (41).

OBESITY, DISEASES, AND MORTALITY

It is widely appreciated that the accumulation of excess calories is associated with an elevated risk of diabetes, myocardial

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>The “Unconquerables”/</th>
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<tbody>
<tr>
<td><strong>Etiologic agent</strong></td>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>One-third of world population infected</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>8–10 million new active cases per year</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2–3 million deaths per year</td>
</tr>
<tr>
<td>HIV-1</td>
<td>33 million living with HIV/AIDS</td>
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<tr>
<td>[Retrovirus]</td>
<td>2.7 million newly infected per year</td>
</tr>
<tr>
<td>Malaria</td>
<td>2 million deaths per year</td>
</tr>
<tr>
<td>Plasmodium falciparum and several other plasmodia</td>
<td>3.3 billion at risk</td>
</tr>
<tr>
<td>[Protist]</td>
<td>250–500 million clinical cases per year</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2–3 million deaths per year</td>
</tr>
<tr>
<td>Orthohepadnavirus HBV</td>
<td>2 billion are infected</td>
</tr>
<tr>
<td>Virus</td>
<td>360 million at risk of chronic illness and death</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>500,000–700,000 deaths per year including</td>
</tr>
<tr>
<td>S. mansoni, S. hematobium, S. japonicum,</td>
<td>hepatocarcinoma</td>
</tr>
<tr>
<td>S. intercalatum, S. mekongi</td>
<td>&gt;600 million at risk</td>
</tr>
<tr>
<td>[Trematodes]</td>
<td>200 million infected; 20 million with debilitating disease</td>
</tr>
<tr>
<td>African trypanosomiasis (Gambian)</td>
<td>100,000 deaths per year</td>
</tr>
<tr>
<td>Trypanosoma brucei gambiense</td>
<td>50 million at risk</td>
</tr>
<tr>
<td>[Protozoa]</td>
<td>100,000 infected annually</td>
</tr>
<tr>
<td>American trypanosomiasis (Chagas disease)</td>
<td>60,000 deaths per year</td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>10 million people infected</td>
</tr>
<tr>
<td>[Protozoa]</td>
<td>20% of infected persons develop Chagas disease</td>
</tr>
<tr>
<td>Syphilis</td>
<td>20,000 deaths per year</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>12 million new cases globally</td>
</tr>
<tr>
<td>[Bacterium-spirochete]</td>
<td>Untreated infection in utero and chronic infection in late</td>
</tr>
<tr>
<td></td>
<td>life can bring devastating complications</td>
</tr>
<tr>
<td></td>
<td>157,000 annual deaths</td>
</tr>
</tbody>
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1 The list is composed of infectious diseases that afflict, or have afflicted, millions of people over a wide geographic area. A distinctive feature is persistence; they are generally incurable without specific modern therapy. In addition to these 8, we call attention to hepatitis C and leishmaniasis as well as the following infestations of helminths, all of which fit this description, infecting many millions: ascariasis (1 billion), trichuriasis (795 million), hookworm disease (740 million), filariasis (120 million), onchocerciasis (18 million), and others. For comparison, diabetes mellitus affects >220 million people worldwide according to the current estimate of the World Health Organization.
infarction, and stroke, as well as dementia, a wide range of other degenerative disorders, and a reduced life expectancy (15, 16). An important link between excess body weight and disease has been ascribed to the metabolic syndrome (insulin resistance, hypertension, dyslipidemia), accompanied typically by proinflammatory processes all over the body that parallel (in most individuals) the course of obesity and its complications (15, 16).

**EVOLUTIONARY PARADOX**

The metabolic syndrome, the link between calorie abundance and inflammation, is present in mice and in rats and in very nearly all humans all over the globe. (The primate line split from rodents 75 million years ago; mouse and rat separated 40 million years ago.) That this energy-wasting, disease-mediating, life-shortening process has had such evolutionary durability strongly suggests that a powerful benefit accrued from the program for countless millennia until recent times.

Our theory (29) is that the metabolic syndrome evolved as an extension of the innate immune system to help the host survive widespread life-threatening infectious diseases, especially “unconquerable” or incurable infections such as tuberculosis, malaria, and trypanosomiasis (see Table 1). The energy-wasting and collateral damage to tissues, undesirable effects of the metabolic syndrome, were acceptable trade-offs when the prevalence of the dreaded infections was high and the typical life span was short. Over the last century, in the wealthier parts of the world, these infections ceased to be lethal threats and the typical life span lengthened; the benefits of the syndrome disappeared, whereas the syndrome’s undesirable side effects were intensified and prolonged (29).

**RECENT REVOLUTION IN INFECTIOUS DISEASES**

Rothstein describes, “one of the most remarkable transformations in the history of mankind. The twentieth century has witnessed the greatest and most rapid changes in both death rates and causes of death in recorded history. At the beginning of the century, infectious diseases were the paramount cause of death in all societies, killing millions of infants, children, and young adults. After 1900, death rates from these diseases declined rapidly in advanced countries, enabling many more people to live to old age” (42; p 71). An increasing number of the elderly died of chronic and degenerative diseases, especially heart disease, cancer, and stroke, which are 3 conditions that are promoted by obesity (43, 44) (Figure 2).

An important corollary to keep in mind is that, throughout history, inflammatory processes with their array of cells, cytokines, chemokines, and reactive oxygen species were largely beneficial in the fight against infectious agents. At the same time, the collateral damage to normal tissue caused by agents of inflammation was relatively inconsequential, especially because of the short life expectancy. The decline in prevalence and the introduction of effective therapies for many infectious diseases along with the extended life span has flipped the equation—the harmful effects of inflammation now typically dominate (29).

**TUBERCULOSIS**

To explain the evolutionary origins and persistence of the metabolic syndrome and the proinflammatory processes associated with obesity, we reviewed the tuberculosis pandemic in 19th-century Europe (29). Tuberculosis was the major cause of death, which exacted an especially heavy toll on reproductive age adults (29). Essentially everyone was infected with the tubercle bacillus. Unlike typical infectious agents (eg, influenza, plague, and smallpox), which have a quick start, finite duration, and prompt resolution (with or without death but often with long-term specific effective immunity thereafter), tuberculosis without chemotherapy is essentially incurable. It seeds the whole body very early in the infection. Sometimes it kills swiftly after initial seeding. It may progress or smolder in localized regions or may live on at intracellular sites solely in latent form, subject to reactivation when the immune system is weakened—by malnutrition, aging, medications (eg, steroids, chemotherapy, anti-TNF agents), and AIDS. Effectively, the infected host spends the remainder of his or her life as a battlefield where the immune system elements of the host are pitted continuously against the infectious agent—with little or no hope for total victory.

**TUBERCULOSIS IS NOT ALONE**

A collection of “unconquerables,” widespread infectious diseases that share some of the special features of tuberculosis, is presented in Table 1 (24–27). Each infects a large fraction of the population in its endemic area. Some are incurable and hardly controllable. With some, the initial infection may be controlled or cured, but the lack of postinfection immunity allows prompt reinfection, a common event given the endemic nature of the disease. Like tuberculosis, the body after infection often becomes a lifelong battlefield. From an evolutionary point of view, these Herculean struggles replayed over hundreds of millennia have left their imprint on the organization of the immune systems of contemporary humans. That the metabolic syndrome with its proinflammatory, antimicrobial features is activated in contemporary humans from all over the world by nutrition-linked signals in the apparent absence of an illness-causing organism at that moment suggests to us that, from a Darwinian point of view, there was a great survival advantage conferred by this program.

![Figure 2](https://academic.oup.com/ajcn/article-abstract/93/4/875S/4597797)
THRIFTY GENES

For almost 50 years, the Thrifty Gene Hypothesis, with its focus on starvation prevention for primitive man, has dominated discussions of energy balance (45, 46). We laud the hypothesis for its innovative thinking when introduced but challenge its focus on starvation prevention. Inspired by Allison’s observation that the sickle cell gene appeared to protect heterozygous carriers from malaria (47, 48), Neel in 1962 propounded the Thrifty Gene Hypothesis to explain the persistence of diabetes mellitus in the population (45). Over subsequent decades, Neel and many others have reformulated this idea, on the basis of each new round of epidemiologic, experimental, and genetic data. Diabetes has been subordinated to obesity as the target of the thrifty genes (46). Instead of a single gene, multiple interacting genes have been postulated. (Many genes are now known to influence obesity and diabetes, each producing a very modest effect.) The hypothesis now posits that the unreliability of the food supply until very recently favored the emergence of programs in vivo that protected against starvation. With the advent of a reliable food supply that is dense in calories and the disappearance of the need for high levels of physical activity, these starvation-prevention programs produce obesity (45, 46). Unexplained evolutionarily is how and why obesity brings on the metabolic syndrome, a calorie-costly pathology-producing add-on. Our theory, which is based on the relentless life-threatening incursions by unconquerable infections, unifies the data much more efficiently.

HIERARCHY OF THREATS TO LIFE

In our opinion, Neel put starvation too high on the urgent list of threats to life. Starvation (a challenge since life began 3.5 billion years ago) takes 2–8 weeks to kill. (Parenthetically, the modus moriendi with starvation is typically a microbial infection. Less often, sudden excessive refeeding kills the would-be survivor.) Water deprivation (a challenge since 0.4 billion years ago) is typically lethal in 3–4 days. Hypothermia (a challenge since 0.2 billion years) can be lethal in minutes or hours. Oxygen deprivation (a challenge since 2.5 billion years ago) can be lethal in minutes. Head trauma and arterial bleeding can be lethal in minutes. Toxins from plants and animals can also kill quickly. Lethal pathogens (a challenge almost since life began) often kill within a few days, but occasionally in hours; with those designated as “unconquerables,” such as tuberculosis, death may occur in days to decades after the onset. Conclusion: among the lethal pathogens (a challenge since life began) often kill within a few days, but occasionally in hours; with those designated as “unconquerables,” such as tuberculosis, death may occur in days to decades after the onset. Conclusion: among the candidates for Horsemen of the Apocalypse, starvation rides a very slow horse.

LOOKING TO THE FUTURE

Let us return to our invited experts who present some leading trends as we seek inspiration in formulating applications to human diseases.

1. Hardie (2) updates us on AMPK, a key enzyme, that immediately responds to a fall in intracellular ATP.
2. Fernandez-Marcos and Auwerx (3) present the latest research on PGC-1α, a transcriptional co-regulator, which has a profound influence on each cell’s mitochondria.
3. Barres and Zierath (4) markedly broaden our appreciation of transcription regulating processes in adults; they show that methylation (and demethylation) of DNA in adults can be very responsive to metabolic influences from within and from the outside environment.
4. Domouzoglou and Maratos-Flier (5) introduce us to FGF21, an emerging hormone-like intercellular messenger, whose most important role may be to help key metabolic tissues respond to calorie deprivation in a coordinated way.

THERAPEUTIC POSSIBILITIES

For obesity and its complications, diet and exercise remain at the top of the therapeutics list. It is gratifying that the expanded knowledge about the molecules that drive appetite and satiety has led to a proliferation of rationally conceived candidate agents, but it is humbling that there are not yet any successful drugs. Optimism still reigns.

One of the main benefits of exercise, even when no weight is lost, is to tone down the proinflammatory processes, especially in the visceral and ectopic fat depots. As the molecular basis of this shift becomes elucidated, we can expect therapies targeting those molecules that will recreate important benefits of exercise—without exercise.

Recognizing that the universe of untapped therapeutic possibilities is vast, we focus on the potential therapies inspired by the invited experts in this symposium. The studies of AMPK, PGC-1α, DNA methylation, and FGF21 (2–5) illustrate 1) the impressive advances in understanding the mechanisms by which the body regulates energy balance and distribution, 2) the rapidly expanding list of molecules and pathways to target therapeutically, and 3) the unexpectedly complex networks of mechanisms.

At a macro level, our top priority would be to extend the search for in vivo molecules that could be targets to pharmacologically disconnect in vivo fat accumulation from the inflammation. This inflammation is a major mediator of pathology in overweight adults and adolescents. Our hypothesis is that the link between fat and inflammation is an evolutionary anachronism that has little or no positive value for residents of the wealthy regions of the world who are no longer threatened by a roster of unconquerable life-threatening infectious diseases. As research defines the links between metabolism and inflammation, this break seems achievable.

If fat-provoked inflammation were to disappear, one obvious side effect of the therapy would be weight gain; the calories now consumed by inflammation would add to the fat stores. Four pathways to dissipate the anticipated surplus of calories seem attractive and feasible in the future, given the direction of today’s research (1):

1. Direct some of the new surplus calories into brown fat: some calories would be dissipated as heat (18–21). The magnitude and consequences of the heat-induced elevation in basal body temperature would put a limit on this pathway.
2. Medications that block the kidney’s glucose transporter (SGLT2) responsible for reabsorption of glucose from the nascent urine would mimic renal glycosuria, a benign condition in which calories are lost in the urine. A better understanding of the cellular distribution of this molecule would improve likelihood of success as a weight-losing agent.
3) A socially acceptable method for increasing purposeless movements (a large fraction of the basal calorie consumption) could be considered.

4) The microbiome of the gut affects calorie balance enough so that its controlled regulation of calorie dissipation could contribute.

CONCLUSIONS

Current research is shedding light on the cellular and biochemical mechanisms that regulate energy balance in vivo. These studies inspire optimism as molecular targets and pathways are elucidated. The growing recognition of the complexity tempers our optimism.

POSTSCRIPT ON HUNGER AND STARVATION

Just a few years ago, as the prevalence of obesity and diabetes continued to increase and that of hunger and starvation diminished, pundits were speculating that, for the first time in history, the number of the overfed will soon exceed the number who are underfed. In recent years, the trend with the overfed continues but the underfed have done an about face. In the wealthy and impoverished nations of the world, the lines on the graphs tracking starvation, hunger, and food insecurity (the official euphemism for hunger in the United States) have clearly reversed direction and turned sharply upward. In the United States, use of food stamps and food banks has hit record highs. The worldwide economic downturn has accelerated this trend. We encourage the nutrition community, while fighting obesity and its complications, to strengthen programs that combat hunger, one of its core missions since the discipline was founded (49).

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