Homeostasis — the Walter B. Cannon’s Legacy — Applied to the Metabolic Syndrome and the Scientific Enterprise

Walter B. Cannon (1871–1945) was a physiologist par excellence, who put to the forefront of medicine the concept that the body responds to external situations through physiological processes that aim to return the body to the steady state. One could argue that, in fact, the physiological responses switch the body from one steady state to another. This wisdom applies well to how our body deals in situations of positive energy balance.

Having been honored by the Walter B. Cannon Award from the American Physiological Society, I have been doing much thinking of how being physiologists could help us look at the ying/yang of health/disease from new perspectives. And certainly the obesity epidemic and its negative impact on health are a good place to start these musings.

Obesity is a major driver of insulin resistance and metabolic syndrome. Classical features of this syndrome are dyslipidemia, abdominal obesity, insulin resistance, and hypertension. It is timely to update this definition to include low-grade, local and systemic inflammation.

Among the consequences of the metabolic syndrome are micro- and macrovascular disease and Type 2 diabetes, along with reduced mobility, loss of productivity, and reduced life expectancy. The cost to health care systems and to the economy are enormous; the cost to the individual’s quality of life can be just as high. Therefore, understanding the metabolic syndrome is paramount, and accordingly there is huge emphasis by scientists, health practitioners, pharmaceutical companies, and governments to attain this goal. Yet, we are far from establishing new strategies that would show any significant change in the vulnerability to the syndrome, its progression, or its devastating outcomes.

It follows that to make deeper inroads in our understanding of the metabolic syndrome and its consequences will require concerted approaches to investigate lipid biology, metabolism, endocrine actions on many tissues, gene associations, and, as realized in the last decade, immunological inputs.

What is Inflammation in the Context of the Metabolic Syndrome?

Briefly, the low-grade inflammation that occurs during the metabolic syndrome is manifest as activation of inflammatory pathways within many cell types. This response is typified by activation of evolutionarily ancient innate immunity programs such as activation of the master transcription factor NF-κB, of the inflammasome, and of other innate immune receptors better understood for their recognition of danger signals associated with pathogens. This has opened numerous questions; for example: Does positive energy balance set the body to present to immune cells cues that are recognized as a danger? Could these danger signals be lipids/lipid metabolites? Components of foodstuff? Products of the microbiota?

A current model proposes that some of these signals within the expanding adipose tissue attract macrophages, which in situ become pro-inflammatory and in turn contribute to insulin resistance of the tissue adipocytes. A similar paradigm has been proposed for muscle and liver. However, the relationship between the immune response to obesity and the consequences of the metabolic syndrome are complex and not absolute. Excess lipids, particularly saturated ones, activate pro-inflammatory pathways in macrophages, and these cells can confer insulin resistance to muscle and adipose cells; but, similarly, lipids can activate inflammatory pathways and cause insulin resistance in the latter cells without contribution of immune cells. In vivo, lipotoxicity and inflammation can occur simultaneously, synergistically, or separately from each other. While multiple strategies to manipulate inflammation improve insulin sensitivity, there are also examples to the contrary. Hence, the relationship among obesity:inflammation:insulin resistance is complex and can both feed forward or be separable from one another.

The steep rise in obesity and Type 2 diabetes observed in the past few decades cannot be explained only on the basis of genetic predisposition. This realization has called for investigation of environmental factors (in foodstuff, water, air, materials) along with changes in behavior (diminished physical activity, diminished sleep hours, elevated calorie consumption, heightened stress, etc.). Some of these factors, typifying prevailing lifestyles in developing/developed countries, activate innate immune responses but can also cause epigenetic changes, and some of these would even have the potential to be perpetuated through the germ line. Quite plausibly, some of the epigenetic changes could arise in immune cells.

How Can We Improve on Our Collective Approach to Understand and Treat the Metabolic Syndrome?

Understanding the origins, incidence, and impact of the metabolic syndrome and combating it effectively will require concerted use of many scientific strategies. In addition to the traditional analysis of alterations in enzymatic activities, signal transduction pathways, gene expression patterns, and acute and sustained responses, one will require immunological scrutiny and epigenetic insight, along with approaches to understand feeding behavior, trends, and pressures (cultural, environmental).

Moreover, since the metabolic syndrome is the result of altered communication among tissues (adipose, liver, pancreas) and the current decade has taught us that factors released by each of these tissues impacts significantly on the others, one will require both “deconstructing” and “reconstructing” approaches to understand organ-to-organ communication ex vivo and in the complex environment of the whole organism.
Because of the huge prevalence of obesity, it is possible that different aspects weigh more in defined groups, families, or individuals. This raises the need to identify cohort-associated changes, and eventually individual-associated changes. The study of the metabolic syndrome thus requires analysis at the level of populations and of the individual. The strategies to analyze each one of these are vastly different. From a health policy perspective, this syndrome lends itself to debating the merits of delivering optimal public health or optimal personalized care.

With the deep challenges posed by the metabolic syndrome to a healthy lifestyle, the time is ripe to design novel, collective strategies that would recruit great minds, novel ways of thinking, and concerted efforts from specialists in different disciplines. Just like major projects in physics and astronomy rely on international teams with specific goals, it is time for all stakeholders in the biomedical research enterprise to realize the need to set aside the individual scientist as the main executor of projects and to focus on the problem at hand and what it will take to solve it. Perhaps tackling the metabolic syndrome could become the beacon for a new way of doing biomedical research: the concerted international teamwork.

As members of APS, we already have a scientific home that could be rallied along to develop a mindset leading to a collective way of doing better science, to achieve better outcomes.

Walter B. Cannon popularized his views in his book *The Wisdom of the Body*. One may say that adaptation to situations and external challenges faces not only the body but also the scientific community, and we must find our new “Scientific Steady State.” The sixth President of the American Physiological Society might have agreed.

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