Why Physiology Matters in Medicine

Physiology as the Underpinning of Medicine

Physiology has a long history of two-way interactions with clinical medicine. Physiology as an experimental discipline emerged in North America during the 1820s as Beaumont studied the gastric secretions of the French-Canadian trapper Alexis St. Marin who had a posttraumatic fistula that permitted easy access to the gastric contents (42, 48). What follows are a few thoughts on why physiology matters more than ever in medicine.

Based on my own clinical experience, the parallels between classic integrative physiology experiments and what happens to patients during anesthesia, in the intensive care unit or in the cardiac catheterization laboratory, seem obvious to even the most casual observer. Additionally, many diagnostic tests like the simple measurement of electrolytes and plasma creatinine are based on the idea that, by simply measuring a few key physiological markers, it is possible to gain insight into the pathophysiology of an individual patient. Physiology is also at the heart of such common tests as the electrocardiogram, simple measurements of blood pressure, exercise based “stress tests,” renal clearance measurements, G1 motility studies, pulmonary function, and a host of others. For each of the examples cited above (and there are many more), there is a clear narrative that shows how physiology as an experimental discipline has been involved in both an intellectual and applied serve and volley with clinical medicine.

It is also interesting to note that standard feedback control diagrams for blood pressure regulation also identify any number of therapeutic targets for treating blood pressure. Recently, new device therapies that target the baroreceptors in the carotid sinus and catheter-based renal denervation have emerged as new approaches to drug-resistant hypertension. Both of these techniques rely heavily on physiological principles (22, 41).

Although the examples noted above represent the conventional wisdom, this conventional wisdom started to shift in the 1980s. Thus coursework in medical school devoted to physiology declined at many institutions, and reductionist disciplines such as molecular biology and genetics were thought to offer the next wave of solutions to clinical problems. A number of high-profile physiology departments either “went out of business” or changed their names to reflect this reality (1, 5).

The Death of Physiology?

So, the idea was that physiology was no longer at the cutting edge of medicine. A few key principles would still be essential, but basically fundamental new insights or approaches to disease were unlikely. Two events exemplify this attitude more than any other. First, in 1989, the gene variant associated with the most common form of cystic fibrosis was identified (10, 35). This led to the idea that, once such changes were identified, gene therapy would be available to fix the genes, restore function, and “cure” affected individuals. One might term this as biological orthopedic surgery. The gene is broken, fix the gene, and cure the patient. In more than 20 years, this vision (with very few exceptions) has produced a series of failures, and it is interesting to note that progress on the cystic fibrosis front revolves mainly around classic “small molecule” drugs that affect the dysfunctional channels in this disease (13, 45). It is of course tempting to speculate that perhaps progress against cystic fibrosis may have been more rapid if more time had been spent on the physiological channelopathy associated with it.

The second major idea was that common diseases such as hypertension, diabetes, and cardiovascular disease would be associated with a limited number of gene variants and that by identifying these variants it would be possible to understand which patients are at risk for which disease. With this knowledge, it would then be possible to effect early intervention before the emergence of major pathophysiological syndromes. In both cases, physiology and pathophysiology would be rendered increasingly less relevant as the molecular causes of whatever ails the patients were dealt with. Unfortunately, the ability to identify specific genetic markers that clearly identify who is at what risk for what disease has been problematic at best (9, 11, 30, 34, 43). For example, the predictive power of traditional phenotypic risk factors is far superior to a genetic risk score for the development of Type 2 diabetes (43). Similar stories can be told about the genetics of cardiovascular risk and also the genetics of Alzheimer’s disease risk (39). Incredibly, extreme aging (FIGURE 1) and also height are not explained by a few common gene variants despite relatively robust heritability estimates based on family studies (4, 46). Additionally, physiological regulation is frequently marked by extreme redundancy, so the fact that a limited number of highly predictive genetic markers has not emerged for common multi-factorial diseases is not particularly surprising (23). So, perhaps if physiology was dying, it was being smothered by reductionist hype vs. being killed by objective data.

Physiology as the Little Engine that Could!

At about the same time physiology was officially dying, a number of physiologically based insights and therapeutic approaches in fact made vast and significant inroads into clinical medicine. Perhaps the most notable example of the continued success of physiology as the backbone of medicine is the discovery of endothelial-derived relaxing factor (EDRF) and the subsequent identification of NO as the main EDRF. The fundamental discovery underpinning all of this was made in an organ bath using isolated blood vessel preparations (14, 15).

The observations that flowed from the EDRF story led to an explosion of new knowledge, including identification of a new family of gas-based biological signaling pathways, new ideas about the role of the vascular endothelium in health and disease, new pathophysiological explanations for a host of syndromes, and new treatments for a number of diseases including erectile dysfunction and pulmonary hypertension. In this context, is it fair to ask whether the discovery of EDRF/NO has had more total impact on clinical medicine than the various flavors of molecular medicine and omics have...
had over the last 30 years? Who knows what the score would be if a strict accounting was in fact done, but EDRF/NO would do very well, especially when one considers the return on investment associated with the initial observations compared with the big science needed to do high throughput “omic” analysis.

Other Examples of the Resilience of Physiology and Medicine

The defenders of the faith in the many flavors of molecular medicine and omics that have emerged will likely discount the EDRF/NO story as blind luck and perhaps the exception that proves their point. However, there are multiple other recent examples of transformational therapies based on physiological insights. Here are a few.

One of the most common causes of death in the world is diarrheal illness in infants and children. This disease can be treated and the victims rescued from certain death with simple oral rehydration solutions based on the fundamental principles of physiological regulation of fluid and electrolyte balance along with GI and renal physiology (6).

Premature birth was once associated with either certain death or an incredible burden of comorbidities in the survivors. The fundamental issue driving many of these problems was the immature lung and a host of complications associated with maintaining gas exchange in premature infants and oxygen toxicity. These problems have largely been solved by a multidisciplinary approach, all based on better physiological management of these tiny humans, along with the development of surfactant therapy to improve ventilation and gas exchange and allow much shorter periods of respiratory support at vastly reduced ventilator settings. Anyone who practiced medicine or nursing in the 1980s and worked with survivors of neonatal ICUs still has a hard time believing

FIGURE 1. Distribution of disease-risk alleles identified from genome wide association studies (GWAS) in long-lived humans (from Ref. 4)

The distribution of these alleles in both familial long-lived individuals and sporadic long-lived individuals was not different than the distribution in control subjects. Conceptually similar analysis paradigms have also shown that the distribution of risk alleles is similar in individuals with and without a number of complex diseases, raising questions about the contribution of many risk alleles to the emergence of specific phenotypes.
just how intact premature babies born in the postsurfactant era are as infants, toddlers, and children (7, 40).

Treatment of coronary artery disease: the per capita age-specific death rates for coronary artery disease have declined by 60–70% since the 1960s. Much of this decline has been due to the therapeutic implications of the simple understanding of the balance between oxygen supply and oxygen demand by the heart (32). This simple relationship has led to highly effective mechanical therapy (surgery, angioplasty, stents), drug therapy (e.g., statins, β-blockers, and other antihypertensives), and other short- and long-term interventions to either improve the balance between supply and demand or prevent it from deteriorating in the first place. The most notable recent examples in this area include incorporation of ideas from the EFRF/NO era into the vulnerable plaque model and the acute coronary syndrome and the effective use of anticoagulants and thrombolytic agents (21, 28, 32).

Use of β-blockers and vasodilator therapy in the treatment of congestive heart failure (CHF). At one time, it was thought that β-blockers would contribute to a worsening of cardiac function in CHF because high levels of reflex sympathetic activity were required to maintain arterial pressure in the face of reduced cardiac pumping capacity. However, via multidisciplinary approaches, it was shown that the high levels of sympathetic activation associated with CHF were in fact part of the problem, and drug regimens designed to blunt the impact of the sympathetic activation associated with CHF have been life extending for many patients. Again, physiological insights and explanations for this problem were key to the development of new therapeutic approaches (8).

A similar story can be told about the Adult Respiratory Distress Syndrome (ARDS). For many years, the goal in critically ill patients requiring mechanical ventilation was to keep blood gases and pH as near normal as possible. This frequently required high tidal volumes and the associated high pulmonary pressures, which resulted in barotrauma to the lung and frequently made matters worse. In this context, more modest levels of ventilation with less than perfect blood gas values have been shown to improve outcomes in ARDS patients, and the explanations for these positive outcomes is physiological (19).

Exercise training is a powerful preventive intervention and treatment for Type 2 diabetes. The improved glucose control evoked by exercise is multi-factorial but has led to a number of insights about insulin-independent glucose transport in muscle and a variety of observations about the physiology of whole body glucose metabolism (20, 26, 37).

What Might be on the Horizon?
The successes noted above are of course very gratifying and give physiologists a chance to say I told you so! However, can new clinical successes dependent on physiology emerge in the future? The short answer is that only time can tell because the nature of medical progress is nonlinear and sometimes counter-intuitive (12). The discovery of EDRF/NO is an example of serendipity, and the emergence of Viagra (which was initially developed as a potential therapy for angina) shows the nonlinear nature of progress. β-Blockers for CHF and kinder, gentler ventilator support in ARDS seemed counter intuitive when first proposed. In this context, a couple of areas seem ripe for improvement by “physiological thinking.” Here are a two.

Alzheimer’s disease (AD) research is focused largely on amyloid accumulation in the brain. However, the epidemiological risk factors for mild cognitive impairment and AD are essentially the same as well known cardiovascular risk factors such as hypertension, diabetes, and inactivity (16, 17, 25, 27, 29, 33, 36, 47). In this context, what is the role of the cerebral circulation, especially the microcirculation in AD? Perhaps AD is merely “brain failure,” and for many other forms of organ failure microvascular dysfunction is a major contributor. Do physiologists have insights that can help find answers and hopefully interventions in AD (2, 3, 38)?

Aging is associated with frailty, and frailty is associated with poor outcomes in older people (31). A key contributor to frailty is muscle loss (sarcopenia). The best current preventive strategies for frailty center around exercise, and the search is already on to understand how aging muscle does or does not respond to exercise and how these responses change with aging (24).

In addition to these examples, the world-wide obesity epidemic clearly has a number of potential physiological explanations that intersect with behavioral science when humans live in low physical activity, high-calorie environments (18, 44). Finally, physiology is informed by concepts like regulated systems, feedback control, and redundancy that operate to keep critical homeostatic variables in normal range. Some of these mechanisms, like baroreceptor resetting, can be hijacked in disease and actually begin to operate in a way that maintains the pathophysiological state in conditions like resistant hypertension. This makes it even more likely that there will not be silver bullets for complex diseases and again highlights the need for more and not less physiological thinking (23).

Summary
In each of the examples of physiological successes discussed in this paper, at least some of the major contributions were made by physiologists. In every case, an integrative physiological narrative aided the process by either providing the pathway to a solution or in the generation of ideas and questions including counter-intuitive questions. These contributions were then amplified by physicians who had a solid understanding of physiology and thus were intellectually ready to integrate new ideas into their own pathophysiological conceptual models. All of this then contributed to progress. Along these lines, if therapeutic progress for complicated diseases is to continue, perhaps the solution is more and not less physiology and more training of future physicians, especially physician investigators, in the “way” of physiology. To many, the idea that more, not less, physiology education and training is needed will seem counter-intuitive, but many physiological questions and approaches in medicine seemed counter-intuitive until the answer appeared.

References
