Physiology is Medicine: Reflections of a Physiologist

La fisiología es medicina: reflexiones de un fisiólogo

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I first started my journey in the discipline of physiology 55 years ago, uncertain whether I wanted to become a physician or a research scientist. At that time, physiology graduate students took the same basic science classes as medical students for the first two years of medical school. My favorite class during this time, one that challenged me most, was a course in pathophysiology focused on 'differential diagnosis'. We were presented with situations where patients described pathological problems in their 'normal' anatomy or physiology that defined a disease or condition and we were then asked to provide a diagnosis and recommended a treatment. For me, this made physiology exciting, relevant and important – a foundation for medicine. But I also came to realize how little we actually knew, which troubled my medical student colleagues who wanted certainty and absolutes but intrigued me as a challenge. Based on this experience and my predilection, I decided to become a research scientist rather than a physician. Since then, I have become the teacher of both anatomy and physiology, two disciplines which I passionately believe are at the core of medicine. In this belief, I am not alone, since it formed the basis for the recommendations of the Flexner Report in 1910 that revolutionized American medical education. The core recommendation of this report was that medical education should be rigorously grounded in the scientific method, with a strong emphasis on combining knowledge in basic science with training in clinical practice in a university setting.

In the early 1900's, the Flexner Report was commissioned based on a need to standardize medical education, which at the time in the United States varied markedly in quality and outcome. The final recommendations of the Flexner Report were based on a solid foundation of best practices that began in Europe in the mid-nineteenth century. A central figure in the revolution in medical education that occurred in the mid-1800's was Claude Bernard, who established the importance of experimental physiology in advancing medicine. By doing so, Bernard and his colleagues demonstrated the value of evidence-based medicine: "The laboratory is the temple of the science of medicine."


Claude Bernard
Founder of Modern Medicine


Walter Cannon
Introduced concept of Homeostasis

In his work, Bernard proposed a key concept in physiology—the constancy of the milieu intérieur, the internal environment. Years later, Walter Cannon elaborated on Bernard's concept in his book The Wisdom of the Body, introducing the term homeostasis. This core physiological concept was based on physical principles of equilibrium thermodynamics and control systems and proposed a state of dynamic equilibrium in living systems. In homeostasis physiological stability must be actively achieved, and our role as physiologists is to understand the complex systems involved including sensors and effectors. Homeostasis applies at multiple levels within our bodies, from intracellular organelles to cells, to tissue, and to the integrated response across the entire body. When homeostasis goes awry, pathophysiology results. Just as Bernard recognized in the 1800's, the key to providing effective medical treatment is to first understand the underlying pathophysiology and where and how things go wrong. To accomplish this, physiologists must work with physicians to explore problems in homeostasis at different levels and translate their findings to provide a better understanding of the underlying pathophysiology and to then provide potential therapeutic strategies to restore homeostasis.

When I am asked "what is physiology" I often reply that there are two major disciplines in biology – structure (anatomy) and function (physiology). Jean François Fernel, the 16th-century French physician who introduced the term physiology to describe the study of the body's function, recognized the interaction between structure and function stating that "Anatomy is to physiology as geography is to history; it describes the theatre of events." In emphasizing the close relationship between anatomy and physiology, Fernel followed in the tradition of the ancient (3rd-century BCE) Greek physicians Herophilus and Erasistratus, who worked at the Museum of Alexandria. They recognized the importance of structure in the function of the human body and made many discoveries that were unfortunately lost until the Scientific Renaissance of the 15th and 16th centuries. In our modern reductionist approach to biomedical research, we often forget the lessons learned from Herophilus and Erasistratus that by exploring the integral relationship between structure and function, we gain a more thorough understanding of physiology and its application in medicine.

In 1981, the Swiss anatomist and physiologist Ewald Weibel working with the American comparative physiologist C. Richard Taylor proposed the concept of symmorphosis, which simply states that the structure and function of biological systems are linked. It is a biological version of the principle of economy of design whereby structure matches (but does not exceed) functional demand. Taylor and Weibel first illustrated symmorphosis in the lung by demonstrating the relationship between the structural determinants of O2 gas exchange (i.e., alveolar surface area) and the functional (metabolic) demands for O2 consumption across a range of species. But the principle of symmorphosis is not limited to the lung and can be applied across all biological systems. This economy of design principle can be scaled to examine the match between structure (anatomy) and function (physiology) at the molecular, cellular, tissue, organ, and whole-organism levels. Morphogenesis is the process that generates shape and form in biological systems, and it has long fascinated biologists. Unfortunately, due to the strong coupling between molecular and mechanical factors, morphogenesis has remained poorly understood. Yet, an understanding of the biophysical mechanisms governing cell shape and movement during morphogenesis is crucial not only during development but for processes underlying wound healing, organ regeneration, and cancer cell invasion, where developmental processes are to some extent recapitulated.

In his book The Blind Watchmaker: Why the Evidence Reveals a Universe Without Design, the renowned British evolutionary biologist and zoologist Richard Dawkins stated that "Biology is the study of the complex things in the Universe. Physics is the study of the simple ones." Dawkins discussed complexity in the context of competing genes forming the basis of evolution—the "selfish gene theory"; however, complexity is the underpinning of physiology and illustrates the need to go beyond a reductionist approach. This is the intersection of physiology (basic science) and medicine. As living beings, we are more than just the sum of our parts (molecules, proteins, cells). Molecular reductionism only provides a description, not mechanisms, underlying function. Physiology as a discipline explores the emergence of function from biological complexity in which the functional properties of molecules and cells emerge only when these parts interact in a wider whole. In discussing the selfish gene theory and biological complexity, the Oxford physiologist Denis Noble makes an important distinction between the components of biology, e.g., genes, ion channels, and the processes that emerge from their interactions, e.g., the coupled rhythms of the heart and respiration.

The discipline of physiology explores the mysteries of life. How is it possible that an organism can live in a dangerous environment, where extreme ambient temperatures, gravitational forces, oxygen availability, or other abiotic factors impose serious challenges to the maintenance of homeostasis? Clearly, our continued survival depends on our bodies being adaptive and resilient. We can explore these physiological adaptations through experiments of nature, where evolution has shaped various strategies to meet environmental demands. Comparative physiologists have the world as their laboratories and the diversity of life as their experimental models. The fascination with life in all its forms relates to our striving for wellness and health. We are all subject to stress, whether self-imposed or in response to our environment.

Our bodies are highly complex, representing the dynamic functional equilibrium of subcellular organelles, cells interacting with surrounding and more distant cells, and tissues and organs interacting with each other. How can we hope to fully understand the biology of our bodies? This is why physiology is fun! Physiological discovery often depends on the development or application of new tools. Disruptive technologies are those scientific discoveries that provide breakthrough capabilities and thereby advance a new paradigm or understanding. Such disruptive technologies can be completely novel inventions or a new combination of existing technologies, but most importantly with an application that leads to a paradigm shift. Disruptive technologies in the commercial world often change our way of life, e.g., the smart phone. Similarly, in physiology and medicine, disruptive technologies create tidal waves that impact and hopefully improve our lives. The introduction of imaging technologies in physiology and medicine is a prime example of such a disruptive technological advance.

In 1895, a German physicist, Wilhelm Roentgen, discovered X-rays almost by accident, and this discovery later earned him the first Nobel Prize in physics in 1901. Within a year after Roentgen's initial discovery, Ernest Codman, a professor of surgery at the Harvard Medical School, applied the novel technology of X-rays to medicine and his surgical practice. One of his first subjects was Henry Pickering Bowditch, the first president of the American Physiological Society and a professor and chair of physiology at Harvard. Bowditch had sustained a wound during the American Civil War, and, 33 years later, fragments of the Confederate bullet in his arm were still clearly apparent in the X-ray image obtained by Codman. This X-ray image was initially viewed by Codman as a novelty and sent to Bowditch as a Christmas greeting. However, Bowditch immediately understood the research and medical potential of this new technology and encouraged his student Walter Cannon to use X-ray imaging in his graduate studies on swallowing. The results of Cannon's initial studies using X-rays to visualize gastric movements were published in the very first volume of the American Journal of Physiology in 1898, only two years after the initial discovery by Roentgen. Since this time, there is no doubt that the introduction of imaging technologies was truly disruptive resulting in a profound influence on physiological discoveries and medical practice.

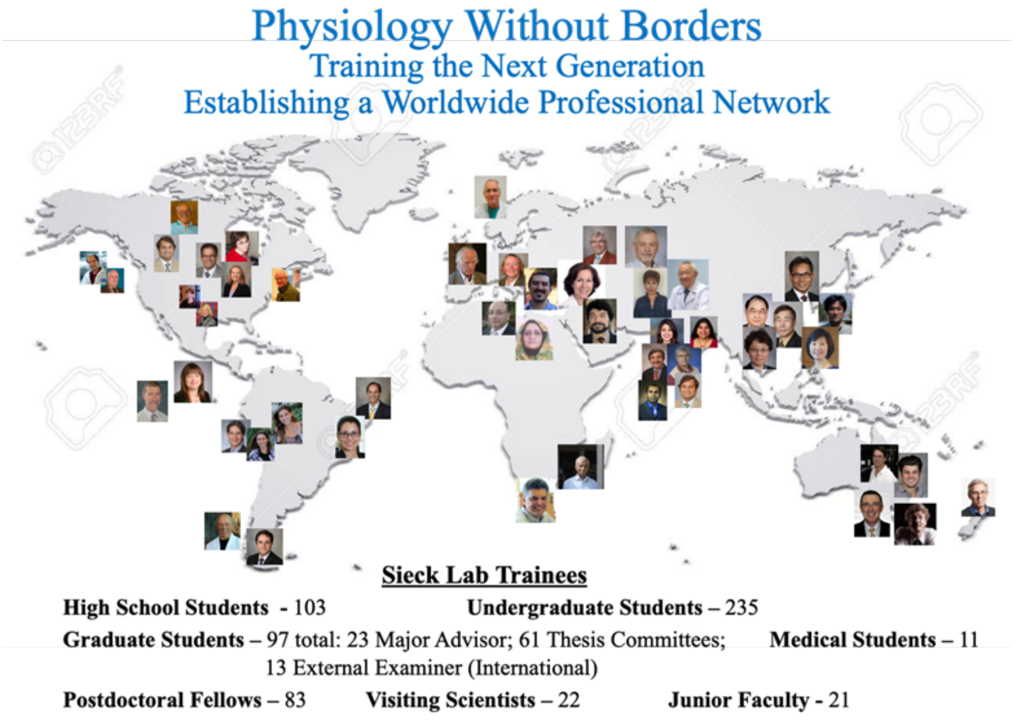
In a similar way, in the past 25-30 years, we have experienced the omics revolution in biology, physiology and medicine with a goal toward individualizing medical care. The transformative technology that led to the omics revolution began with the discovery of the helical structure of DNA by James Watson and Francis Crick in 1953, for which they were awarded the Nobel Prize in 1962. Subsequently, Frederic Sanger and colleagues described the amino acid sequence of insulin in 1955 and developed the initial technologies for gene sequencing. Thereafter, several variations of the Sanger method for gene sequencing were introduced, and, although they were an improvement, these procedures were still very limited. For his groundbreaking work in the sequencing of nucleic acids, Sanger shared the 1980 Nobel Prize in chemistry with Walter Gilbert and Paul Berg. The introduction of gene-sequencing techniques initiated several genome-sequencing projects that progressively increased in intensity and scale. The Sanger gene-sequencing method was also termed "shotgun" sequencing and was better suited for analysis of longer DNA sequences necessary for description of entire chromosomes. The "next generation" gene-sequencing technologies built on the fundamental technique of Sanger to provide faster, less costly, and higher-resolution gene sequencing for larger-scale genomic analyses. There is no doubt that these gene-sequencing technologies represented a paradigm shift for physiology and medicine. However, with these transformative imaging and gene-sequencing technologies, there has been an explosion of information and the dawn of "new" disciplines of "systems biology" and "bioinformatics" that build on mathematical and modeling skills to allow interpretation of these large complex data sets. We are now experiencing a new artificial intelligence revolution to address the explosion of complex information that will require the application of advanced computational methods and statistical modeling to allow interpretation. As physiologists, we are well prepared to apply these novel technologies and computational tools to explore the complexity of our bodies.

As physiologists using these technologies and tools, we are only beginning to understand the complex interactions between the environment and our genetics, and how these interactions impact our daily and future lives. Events that occur early in our lives can mold our future development and change how we respond to the environment or mitigate our susceptibility to disease. What marvelous complexity we explore as physiologists, unraveling the mysteries of life—this is too much fun to be work! As a physiologist, I saw the challenge of complexity early in my career, and I've pursued it for more than 50 years. Importantly, I've been guided by my interactions with scientists and physicians around the world who have helped interpret physiological complexity into practical solutions.

My studies have primarily focused on the physiology of respiration. The breath of life is a primitive concept forming the basis of many religions and philosophies. In ancient Greek medicine, pneuma was a form of circulating air that was necessary for our body's normal function or physiology. In the 3rd to 4th century BCE, the Greek physician Herophilus recognized that there are structural differences between arteries and veins, and he attributed the pulsations in arteries to the pumping action of the heart. He also recognized that the inhalation and exhalation motions of the chest wall and lungs reflected movement of air into and out of the lungs. His student Erasistratus, as with all good students, took the observations of Herophilus one step further by recognizing that valves in the heart allowed blood flow in only one direction, and concluded that the right and left sides of the heart were separate but connected unidirectional pumps. On the right side, he noted that blood flowed to the lungs through the pulmonary artery. He postulated that, during inspiration, pneuma was drawn into the lungs through the mouth, nose, trachea, and bronchi. In the lungs, pneuma was then drawn into the blood by ventricular diastole, where it was mixed and then distributed from the left ventricle to the aorta and then the rest of the body. Unfortunately, this remarkably enlightened understanding of cardiopulmonary physiology nearly 1,800 years before William Harvey's "discovery" of blood circulation was muddled in the following centuries by the profound influence of the 2nd-3rd century physician Galen on medical thought. According to the doctrine formalized by Galen, the movements of respiration served three purposes: 1) to inhale air to cool and regulate the innate heat of the heart; 2) to mix air into the blood, which was necessary to generate pneuma that was then distributed from the left side of the heart throughout the body via arteries; and 3) to eliminate "friligimous," the foul vapor byproducts of the innate fire in the heart. Even during Herophilus's time, it was recognized that blood in the arteries and veins differed in color, which Galen attributed to the difference in pneuma vs. friligimous foul vapors. The primary function of respiration in O2 and CO2 gas exchange remained unknown for 1,500 years until modern empirical method of discovery was re-introduced by Robert Boyle and others, which provided a better understanding of the physical chemical nature of gas. This enlightenment is summarized by Boyle "God would not have made the universe as it is unless He intended us to understand it." It is fitting that this important bridge between the Scientific Revolution of the 1600's and the Enlightenment of the 18th-19th century had a profound impact on our understanding of how and why we breathe.

As a physiologist, I have been able to pursue my curiosity, and I never tire from the excitement I feel in making discoveries. I think this is natural, since almost everyone I know is curious about how their own bodies work or how the bar-headed goose can fly over Mount Everest or whales can navigate the oceans. Even though not recognized, physiology surrounds us and occupies our thoughts. When I exercise (and yes, I know I should do more), I am curious about how my body adapts and how I can perform better. As I grow older, I am curious about physiological resilience and how my body regenerates (or not) from things like exercise. When I experience air pollution or hear news about global warming, I am curious how this affects wildlife big and small. Even if I had not pursued a career in physiology, I would still be curious about my body, my environment, and the living world that surrounds us.

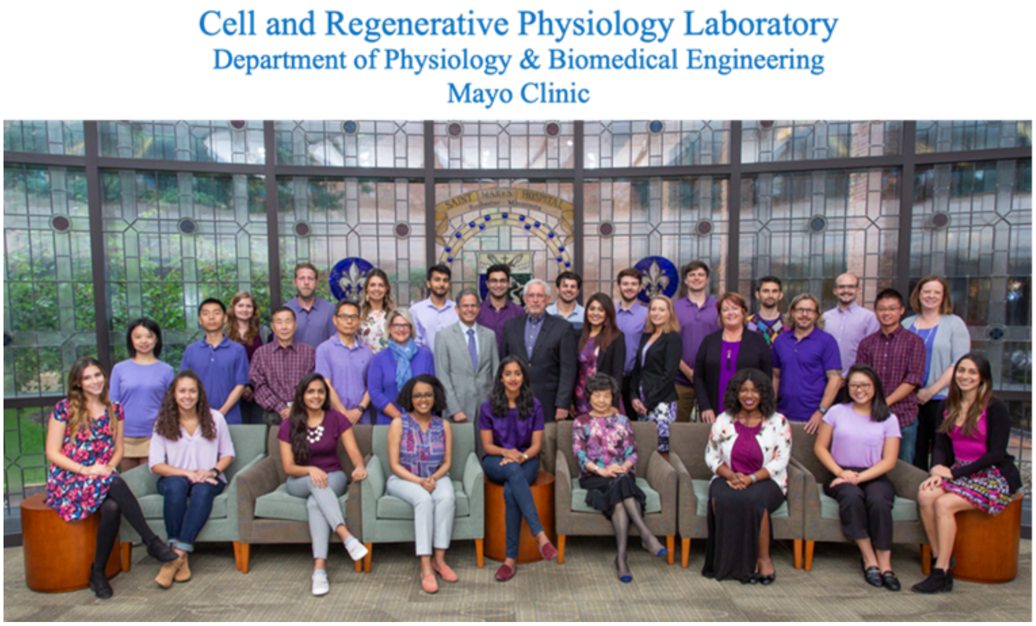
As a physiologist, I have spent my entire career as a perpetual student incessantly pursuing my curiosity with a passion, using my imagination freely, and making new discovering about life. Albert Einstein clearly understood the central role of curiosity in science and discovery when he wrote "I have no special talents. I am only passionately curious…" noting that "the important thing is not to stop questioning." As a scientist, by exploiting my curiosity and imagination, I am fortunate to realize the rewards of discovery. I am also fortunate that my family, friends, and colleagues have nurtured my passion for science, exploration and discovery. For me, my "job" is not work it is my life! I cannot think of a greater profession, and I have enjoyed every moment. I hope that my passion for understanding life function has ignited curiosity and imagination in others in their pursuit of new knowledge.


Physiology Without Borders
Training the Next Generation
Establishing a Worldwide Professional Network

Sieck Lab Trainees

High School Students - 103
Undergraduate Students – 235
Graduate Students – 97 total: 23 Major Advisor; 61 Thesis Committees; 13 External Examiner (International)
Medical Students – 11
Postdoctoral Fellows – 83
Visiting Scientists – 22
Junior Faculty - 21

A map illustrating the global professional network founded by Dr. Gary Sieck, inspired by the guiding concept of 'Physiology Without Borders'.



Physiology Laboratory led by Dr. Gary Sieck at the Mayo Clinic, Rochester, United States.