Physiology, reductionism, and translational medicine: the right mix

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We the Editors of the American Journal Physiology: Lung Cellular and Molecular Physiology were delighted to be able to read (4) comments on the current status of physiology by Dr. Michael Joyner, Mayo Clinic, Rochester, MN, that were originally communicated as part of his Edward Adolph Lecture at Experimental Biology 2011 meeting. Dr. Joyner’s views add to his previous energetic and intellectual efforts (5–7) to bring to our attention the counterproductive confrontation of reductionism and physiology. Dr. Joyner’s provocative style does not detract from the importance of the topic; this is underscored by the simultaneous appearance of editorials by Drs. Peter Wagner and David Paterson in Journal Applied Physiology (11) and Journal of Physiology (12) inspiring us to be more proactive in support of our discipline.

Dr. Joyner (4) briefly outlines trends in the disciplines of life science and biomedical research that initially popularized (as evidenced by attraction of scientists and sources of support) reductionism (via advances in molecular biology, biochemistry, and genetics) and subsequently systems biology. He provides several examples that underscore the collective inability of these approaches to move discoveries from bench to bedside at a pace predicted by their proponents and contrasts this to the continuous, effective, and timely ability of traditional physiology to affect progress in clinical medicine. Much of the ineffectiveness of reductionism and systems biology is attributed to limitations of these approaches at a cellular level, including lack of inclusion of principles of homeostasis, regulation, and redundancy that are synonymous with integrative or traditional physiology. The arguments are well stated, and numerous examples in cardiorespiratory and metabolic systems are provided to support the contention that basic principles of physiology remain the enabling tools and technologies to advance understanding of human biology and medicine.

In developing this thesis, Dr. Joyner downplays reductionism by juxtaposing italicized quotes from leading scientists regarding the promise of the completion of the Human Genome Project (HGP), gene therapy [for cystic fibrosis (CF)], and genome-wide association studies (GWAS) with a cursory review of the failures and/or limitations in these areas to date. With noted exceptions of pharmacogenomics and anthropology, molecular reductionism is packaged as a disappointment and its failures are portrayed as the motivating force for the current trend of developments in systems biology. The ambiguities in definition of systems biology and its redundancy with traditional physiology along with its apparent restrictions to a cellular level (6) and its gene-centered (9) approach underscore the uncertainty as to whether this approach is the integrated science that will subserve the needs of translational and other future efforts. This is contrasted to the remarkable success in the last 20–30 years of traditional physiology in revealing the role of nitric oxide in vasomotor regulation, application of ventilator strategies in critically ill patients that reduced mortality (1), use of β-blockers in congestive heart failure, oral rehydration in diarrheal disorders, and exercise in type 2 diabetes. Drs. Wagner and Paterson (11, 12) remind of us of the historically awkward transitions in incorporating molecular techniques into more traditional physiological approaches but suggest that sufficient forces are at play now for reductionists and physiologists to interact in a rational and purposeful fashion.

An important concept that emerges from Dr. Joyner’s lecture (4) and the accompanying editorials (11, 12) is poetically portrayed by the phrase and title of another recent opinion by Dr. Joyner (6), i.e., “physiology, alone at the bottom, alone at the top.” In this regard, it is apparent that physiology sits uniquely between genes and clinical care and between molecular biology and epidemiology. It is the enabling technology to advance pharmacotherapeutics and the critical quantitation of phenotype that informs us of etiology and underscores diagnosis and therapy. For example, provocative testing is a hallmark of medical diagnosis. Collectively, then, it is curious how endangered physiology has become as is reflected in somewhat whimsical changes in the names of basic science departments and the apparent decline in formal training. In this regard, advocacy strategies for physiologists have been outlined by leaders of the American Physiological Society (11, 12) and the International Union Physiological Sciences (9).

Although advances in molecular biology and their impact on reductionist approaches and systems biology are as diverse, painstaking, filled with serendipity, and time consuming as other disciplines in life science, the historical milestone of the publication of the initial sequencing and analysis of the human genome (3) demarcates the beginning of a 10-year interval for us to consider its influence (8). The enormity of the effort and its intrigue and competitive nature made it susceptible to overzealous expectations as well as harsh criticism and disappointments. As such, a number of highly authoritative reviews (8) and commentaries have recently appeared on the tenth anniversary of this milestone to put in perspective the impact of this effort in human biology. There are readily demonstrable extraordinary advances from the HGP that indeed have a significant impact on clinical medicine in addition to new insight into the structure and function of human genome.

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Dismissing these advances is convenient for portraying the provocative stance that advances in medicine can only emerge with physiology. By contrast, recognition of the enormous impact of the HGP will get us closer to achieving a productive interaction of the physiological and genomic studies.

Prior to the HGP, cumbersome genetic linkage mapping in affected families had revealed <100 disease genes. Within less than 10 years subsequent to the HGP, the number of disease genes that have been identified has grown to 2,850 (8). These efforts have led to important diagnostic protocols and suggested unique physiological pathways, some of which may be amenable to small molecule therapy (e.g., Marfan’s syndrome and angiotensin II receptor blockers for TGF-β dysfunction). Pessimism regarding the predictive powers of genes and especially GWAS has been dispelled by newer genomic statistical and theoretical approaches to common disease-common variant hypotheses, and there are now over 1,100 confirmed genetic loci affecting polygenic disorders including dyslipidemias, Crohn’s disease, type 1 and type 2 diabetes, and others. Although currently this approach is less persuasive in determining risk of disease (and personalized medicine), it is clear that the study of common diseases and their traits has revealed new and important signaling pathways that may be amenable to pharmacotherapy (8). Furthermore, despite Dr. Joyner’s statements to the contrary, a number of cancer genes and their predicted signaling pathways have been identified with genomic approaches, and understanding of the heterogeneity of tumors, small molecule therapies, diagnostics and clinical trials has truly accelerated. Indeed, current concepts on tumor microenvironment and information gleaned from genomics have contributed to unifying physiological approaches to various tumors (2).

Dr. Joyner speculates that progress in CF (and other diseases) may have moved faster if genomic efforts did not distract from traditional physiological and pharmacological approaches. He couples this notion with a discussion of the disappointments of gene therapy and highlights the potential irrelevancy of knockout mouse experiments. These are important lessons for pulmonary physiologists and, in fact, highlight the need for close linkage between traditional physiology, genomic sciences, and translational medicine. It indeed is an accurate depiction that the excitement about potentially curing cystic fibrosis with gene replacement that occurred shortly after the identification of mutations in the cystic fibrosis transmembrane regulator (CFTR) gene was a temporary distraction in CF research. It is also clear that the initial excitement in engineering a CFTR-null mouse was ultimately lessened by important differences between murine and human airway epithelium. Nonetheless, a strong argument can be made that progress in the disorder is a direct outcome of 20 years of genomic research and reductionism along with expert physiological approaches. In retrospect, it is reasonable to assume that a monogenic disorder such as CF would be a strong candidate for rapid translation of genomic information into clinical medicine, and in many ways the enormous progress in 20 years is consistent with this. However, the lessons learned from the process of identification of the gene to physiological and phenotypic understanding of its normal function and effects of mutations are a sobering reminder of the complexities of human biology. In this sense, the contribution of physiology is assured, and in many ways the stops and starts in CF research are a purposeful and useful demonstration of the need to integrate physiology with genomics and reductionism.

The American Journal of Physiology: Lung Cellular and Molecular Physiology remains dedicated to our efforts to publish original articles covering the broad scope of molecular, cellular, and integrative aspects of normal and abnormal function of cells and components of the respiratory system. The Journal was established during the transition period in which molecular biology and subsequently intensive genomics became so influential in our approach to lung biology. As such, we espouse the spirit shared by Drs. Joyner, Wagner, and Paterson that advances in medicine will only occur with an integrated and interactive effort among reductionists, systems biologists, and physiologists. We hope that the Journal serves as a practical focus for advocacy efforts for the physiological sciences in lung research. We share concerns that every attempt should be made to increase the speed of translation of findings in pulmonary biology to pulmonary medicine. Nonetheless, progress has been remarkable, especially if the landmark is the 10-year anniversary of HGP. The tools provided by molecular biology and genomic science are vital to further hasten transfer of information from bench to bedside and back.

REFERENCES