COMMENTARY

Perspectives

If it's not integrative, it may not be translational

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If 1 or 2 descriptive terms were to be selected to characterize the major thrusts in medical science and clinical medicine during the last decade of the 20th century, they would be "genomics" and "evidence-based medicine." These terms would reflect, on the one hand, the dominance of cellular and molecular biology in basic scientific research during the 1990s, driven largely by the spectacular advances in molecular genetics, and, on the other hand, the ascendancy of epidemiology and health services research as the dominant forces in clinical medicine, driven largely by reforms in health care delivery.

Although genomics and evidence-based medicine will undoubtedly continue as powerful forces in medicine in the early 21st century, there is a discernible shift in momentum toward that domain of inquiry termed "translational research." In broad terms, translational research defines 2 processes:[1] the application of advances in basic science to the diagnosis, treatment and prevention of disease, and the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory. Thus, translational research involves transfers from bench to bedside (and population) and from bedside to bench. A necessary requirement, therefore, in the process of translational research is that the investigator be literate in at least 2 "languages." In the transfer of knowledge from the bench to the bedside, one of the critical languages through which the translation must pass is that of integrative biology (also referred to as clinical physiology), the branch of science that deals with synthesis and integration at the systems level. Ultimately, this process requires studies in the intact organism, where the complex interactions of genetic, biochemical, physiological, behavioural and environmental influences are brought to bear. Because this type of investigation often involves studies in humans, it is frequently classified under the broad heading of "clinical research," together with clinical epidemiology and health outcomes research. Although the semantics per se are not important, the differences between integrative biology and clinical epidemiology are obscured by the term clinical research, which may therefore not serve either discipline well. Indeed, the differences in experimental methods between these 2 domains of science are as great as those between integrative and molecular biology. Integrative biology generally involves in-vivo observations, measurements and manipulations in intact animals and humans, in contrast to cellular and molecular biology in which studies are conducted largely in vitro (even if the materials are derived from humans), and in contrast to clinical epidemiology and health services research in which studies are generally conducted at the cohort or population level on databases that may include observations and measurements derived from human subjects but not typically direct experimental manipulations. Perhaps the most distinguishing characteristic, therefore, of integrative biology is that it involves direct investigator contact with patients, unlike the other 2 domains of science.

The role of integrative biology in translational research can perhaps be best understood by reference to a common clinical problem: hypertension. A very useful approach to defining the fundamental causes of hypertension has been the investigation of rare familial forms of blood pressure variation in which mutations in single genes result in either very high or very low blood pressure. Close to 20 such mutations have now been identified.[2] However, given the diversity of physiological systems that interact to

influence blood pressure (including baroreflexes, natriuretic peptides, the renin-angiotensin-aldosterone system, the adrenergic receptor system, and endothelial-derived vasoactive mediators such as nitric oxide and endothelin), the identification of genetic mutations that are associated with variations in blood pressure does not in itself provide insights into the physiological mechanisms that are disturbed by the genetic defects. On the contrary, it is only with detailed integrative biologic studies involving experimental manipulations (such as salt infusion and diuretic administration) and physiological measurements (such as blood pressure, salt excretion and renin levels) that the specific pathways affected by the genetic mutations can be defined. Interestingly, it turns out that despite the physiological complexities involved in blood pressure regulation, detailed in-vivo studies in humans and in animal models indicate that *all* of the known genetic mutations associated with severe hypertension and severe hypotension act through a single common physiological pathway in the kidney, resulting in either a net increase or decrease in salt reabsorption,[2] a concept with important therapeutic implications. Furthermore, based on these insights, it is intriguing to speculate (but of course, does not necessarily follow) that all forms of "essential" hypertension in the general population will turn out to be the result of alterations in renal salt balance. However, it is only by means of integrative biologic studies in people whose genotype has been carefully defined that this question will be answered. Nevertheless, the hypertension story to date provides a compelling example of the notion that "far from molecular biology 'explaining' physiology, physiology will be totally necessary for an understanding of what all the molecular biology means."[3]

The power of integrative biology in translational research is not limited to defining the relationships between genotype and phenotype but also plays a critical role in informing and interpreting epidemiologic studies. To continue with the blood pressure story, in those with genetic mutations that result in hypertension (as a result of increased renal salt reabsorption), there is a *direct* relationship between daily salt intake and blood pressure: the higher the salt intake, the higher the blood pressure. In contrast, in people with genetic mutations that result in hypotension (as a result of decreased salt reabsorption), there is an *inverse* relationship between daily salt intake and blood pressure: the higher the salt intake, the lower the blood pressure.[4] The basis for this paradox becomes clear when the independent and dependent variables in the relationship are understood. In the hypertensive subjects, a high salt intake results in higher salt reabsorption, and therefore in higher blood pressure. In contrast, in the hypotensive subjects, those with the lowest blood pressure (as a result of defects in salt reabsorption) have learned to consume large amounts of salt in order to maintain their blood pressure; hence, the lower the blood pressure, the higher the salt intake. In the first case, salt intake determines blood pressure; whereas in the second case, blood pressure determines salt intake. If, for the sake of argument, the genetic mutations associated with high and low blood pressures were distributed with equal frequency in the general population (but these genetic and physiologic distinctions were unknown), an epidemiologic survey of daily salt consumption and blood pressure levels in the population would lead to the conclusion that there is *no* relationship between the 2 variables, given that in one group the relationship would be direct and in the other group it would be inverse.[4]

Thus, what is true for molecular biology is equally true for clinical epidemiology; namely, that without the insights provided by integrative biology, the associations (or lack of them) identified in epidemiologic studies may defy interpretation. The issue, therefore, is not whether integrative biologic research is of greater or lesser importance than cellular or molecular and epidemiologic research (a rather meaningless debate), but rather that advances in translating knowledge from the bench to the bedside and to the community (and vice versa) will require the incorporation of integrative biologic approaches into the research enterprise. Indeed, the notion of the 1990s, prevalent among many basic scientists, clinician-scientists, granting agencies and clinical journals, that "if it isn't molecular, it isn't science," should perhaps be replaced by a more current reality that "if it's not integrative, it may not be translational."

Given the important role of integrative biology or clinical physiology in translational research and the

unique role played by clinician-scientists in this investigative domain, the relative paucity of clinician-scientists involved in integrative biologic research should be of particular concern to academic medicine and to the broader scientific community, including funding agencies. The reasons underlying the decline in numbers of "patient-oriented" clinician-scientists during the past 20 years were discussed recently in this journal.[5] The most important of these reasons perhaps has been that the last decades of the 20th century were indeed the era of "genomics" and of "evidence-based medicine"; and neither surprisingly nor inappropriately, these drove the career choices of a generation of clinical investigators. As a result, to quote the director of research training in a prestigious United States Department of Medicine, "we have produced a generation of clinician-scientists who can clone the genes underlying human diseases and who can produce animal models containing these defective genes, but we have no one left who knows how to study the development of the disease phenotype in these animal models, let alone in intact humans."[6]

The challenge, therefore, to academic clinical departments is clear. While maintaining strong research thrusts in both cellular and molecular biology and in clinical epidemiology, we must ensure that integrative biology also flourishes in our universities, teaching hospitals and research institutes, if the advances of basic and epidemiologic science are truly to be translated into advances in understanding human disease mechanisms, diagnosis, treatment and prevention. This mandate will require that we highlight integrative biology as a potential career choice for clinical trainees pursuing academic careers and that our recruitment policies reflect recognition of the central role of integrative biology in the translational research pathway. Clinical departments have a particular responsibility in this regard, because integrative biology is the one domain of science that is critically dependent on the participation of physician-investigators and patients. Given an understanding of the need and a commitment to discharge our responsibilities, the Canadian academic medical community must marshal the necessary resources and ensure that physician-scientists play a leading role in the important "translational" challenge that has now engaged medicine and science.

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