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Physiologists……….on the List of Endangered Species?

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ABSTRACT: Physiology is the science of life that deals with the ability of a living organism to maintain stable internal environment and normal function in the presence of changing external environment. Is it true that physiology has become "an old science" and is a dying discipline? This article addresses the problems faced by physiologists with regard to the concepts of reductionism/integrationism, and how technology breakthroughs that once divided body function into separate levels of organization, are now bringing together the jigsaw pieces to be assembled into a one big beautiful and complex whole. That last crucial part is undoubtedly the role of physiologists. So, it may be that "Integrative Physiology is the biology of the future".

KEYWORDS: integrationism, multidisciplinary research, physiology, reductionism.

WHAT IS PHYSIOLOGY?

As stated by Claude Bernard, in his opening lecture of a course in general physiology at the Museum of National History in 1870, "**Physiology is the science of life":** it describes and explains the phenomena and characteristics of living beings. Defined thus, physiology has a problem which is peculiar to it, and which belongs only to it. Its point of view, its goal, its methods make it an autonomous independent science". According to Claude Bernard, the prerequisite for the existence of organisms independent of the external environment was the stability of the *"milieu interieur"* or the "sea within". Conceptually, it was the ability to maintain stable internal environments and normal function in the presence of changing external environment. In 1932, Walter B. Cannon introduced the word **"homeostasis"** which became the identity of Physiology. To give a clear simple picture of the meaning of homeostasis, Stanley G. Schutz explained it this way : "How can we eat what we want, drink what we want, live where we want, do what we want, vary our metabolic rates over a five fold range, and stay the same within very narrow limits? And if we stray much beyond these limits, we die!"[1]. Physiology was then regarded as the fundamental foundation of medical science. I suppose this is still true in a way, as one of the Nobel Prizes is called the Nobel Prize in Physiology or Medicine. But the present career path of physiologists is far from being an eight lane-highway.

IS PHYSIOLOGY DYING?

Over the following decades, physiology gradually became known as "an old science" that encompassed different body systems, namely, the nervous system, musculoskeletal system, cardiovascular, respiratory, renal, gastrointestinal, reproductive and endocrine systems. Students' interests in the discipline dwindled, so did its share of research support. Eventually in the late 1980's, it lost one important area. Neurophysiology was lost to the new discipline of Neuroscience, which emerged from the integration of different approaches to the nervous system function, from cellular and molecular biology to system analysis and behavioural science[2]. Things became more serious. In 1997, News in Physiology published an article entitled **"Is Physiology a dying discipline**?"[3], which reflected the sentiment and concern of physiologists worldwide about the future of physiology, as a discipline.

As G.G. Pinter and Verla Pinter[3] commented, "While interest in and support for old systems physiology declined, there was a more than compensatory increase in cellular and molecular biology". Molecular biology, a spin off of biochemistry, resulted from the strong prevalence of reductionistic research together with advances in methodology. There is no doubt that molecular biology is a powerful and valuable tool for hypothesis testing. However, when it comes to using molecular biology to establish "fact", there is ground for concern, since being a truly reductionist, molecular biology focuses on a singular problem (which is its strength) and presents qualitative or semi-quantitative "findings" that are accepted by many as "knowledge". Nevertheless, the excitement and enthusiasm that greeted reductionistic molecular biology and molecular genetics, and the current of information that flowed out from these disciplines literally swept the old science off its feet, pushing it down the priority list of funding agencies. The danger was too real- in1980's, so that a number of departments of physiology in North America disappeared, changed their names, or merged with one another to become a more marketable Department of Physiology and Biophysics or Department of Cellular Physiology. Even a Ph.D. graduate in physiology (with a thesis entitled "Coenzyme X induced differentiation in cell line YYZ/2 by turning on gene.........") could not explain how the cardiovascular system responded to exercise and had no clue how to anesthetize an experimental rat. Even now, there is no denial that it is difficult for physiologists to get their *in vivo* results published even in physiology journals without supporting evidence from cellular or molecular studies. Is Physiology a dying discipline?

To turn foes into friends

Reductionism refers to a belief that the property or behaviour of a composite system can be predicted or understood from an understanding of the properties or behaviour of its constituent parts studied in isolation[1]. In other words, the property of the whole is the sum of the property of each isolated part. However, in the biological world, the whole is often greater than the sum of its parts. Sometimes, the property of the whole system cannot be deduced from the properties of the constituent parts. This is the concept of **Integrationism.** Our body is not a simple composite of organ systems, which in turn are composed of cells. Its organization involves regulatory systems, chains of command and feedback loops that are interconnected in such a way that the body functions as a complex whole with certain properties identifiable only at the whole body level.

No one will deny that molecular biology and the new imaging techniques open up areas which were previously inaccessible to physiologists. These new approaches become valuable tools for exploring certain levels of organization and studying parameters not measurable before. Professor Bjorn Folkow at the University of Goteborg, Sweden looked at our body as being composed of six levels (Figure 1), whole body, system level, organ level, cellular level, subcellular level, and molecular level[4]. He celebrated the breakthroughs in molecular biology, but reminded us that "above the cellular level come the infinitely more complex hierarchies of function and control that characterize higher organisms. Each of these six levels of biological organization is important in its own right and their respective explorations demand specialized approaches and methodologies, different kinds of investigators with characteristic ways of thinking and reasoning". Physiologists alone are responsible for unraveling the mystery at the levels I-II-III, without which higher organisms will never be understood.

With the above realization, physiology can survive by becoming truly integrative not only in the sense of integrating information from different body systems, but by integrating the research approach with those of other disciplines. Of utmost importance, physiologists should not be made to jump in and get swept up by the wave of enthusiasm to levels IV-V-VI and abandon their own levels I-II-III. In reality, it is not enough to stand their ground, they desperately need to work against the current and to convince the scientific community that complete knowledge of the higher organism that ultimately leads to understanding of the underlying mechanism of diseases, their treatment and prevention requires total understanding of all six levels, each level on its own, and when they are in assemblage. No matter how difficult and time consuming the study of levels I-II-III is, it is the only way into an understanding of whole tissues, organs and organisms.

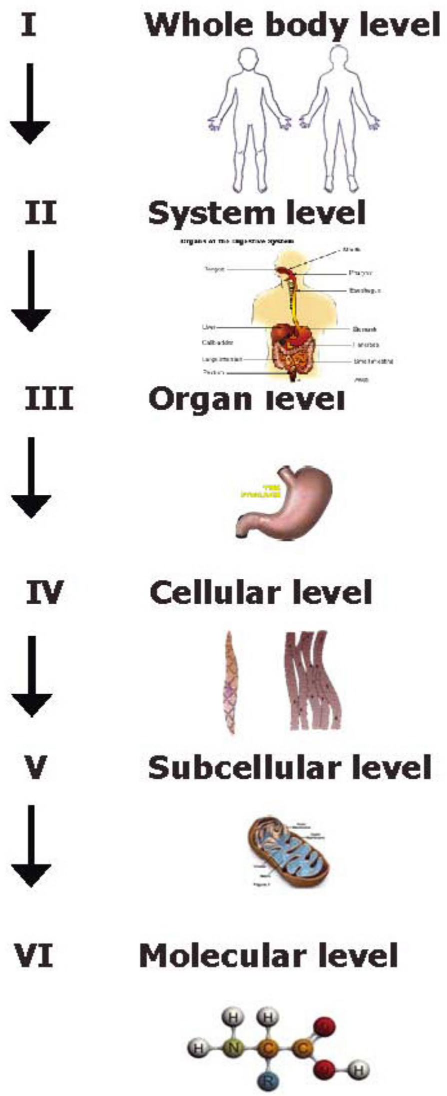

Fig 1. Schematic outline of 6 main levels of hierarchial organization and control in higher organisms (modified from reference 4).

The tide is turning

There is no better time than now to appreciate the significance of physiology as a science. Research problems can arise from any level of organization, waves of investigations propagate in both directions, towards level I and level VI. With the explosion of information as a result of technology breakthroughs, cellular and molecular biologists are at the stage of searching for the meaning and significance of their findings from genomic and proteomic research. These scientists will be looking up from the depth of the organization levels to the upper levels of biological significance. The 'stick' is going to be passed on to the next runner to carry to the finish line.

There is no better time than now for physiologists to get ready for their 'omic' era. Are they ready? They need to convince the academic institution and granting agency that systems physiology is most essential for establishing the significance of findings from other disciplines. Individual pieces need to be put together to complete the jigsaw puzzle. "The difficulty stems not only from the fact that the number of parts is huge, but also and far more importantly, from the fact that, in biology, the parts are dynamic and plastic"[1]. There is need to convince physiologists themselves that whichever level of organization they focus their work on, they should relate their findings to the process at another level. For instance, if one is investigating the effect of a hormone on ion transport across the cell membrane, one should pursue one's study upward to explain hormone function at the organ level. At the same time, one should study in depth to demonstrate the intracellular signaling pathway or the genomic action of the hormone. The bottom line is that physiologists must be more flexible and adaptive because **"Integrative physiology is the biology of the future"**

One recipe for survival

For this part of the article, I would like to use my own experience at the Department of Physiology, Faculty of Science, Mahidol University to show how a small one supervisor-one student laboratory may evolve into a multidisciplinary laboratory and a research consortium. Frankly, it initially evolved not as a result of a brilliant foresight but out of necessity.

I consider myself very lucky in many ways (that will be pointed out as I go along) to be where I am now. First, I was lucky to have my thesis supervisor and mentor, Professor Liangchai Limlomwongse to show me how to think like an integrative physiologist right from the beginning. I started off like most physiologists did, and many still do, as a small laboratory, working on a topic that was a continuation of my Ph.D. dissertation, a topic far from being glamorous, high impact or a hot issue. It was a small basic science project with a clear objective. My work focused on the action of the hormone prolactin on the intestinal absorption of calcium. Using the same approach and methodology and with the help of my mentor and my students, I started to build up my curriculum vitae, which in turn helped bring in some small grants. For a physiologist, having picked calcium metabolism as a research area was a blessing in itself in that besides working on the whole body level, one was automatically forced to become familiar with the other major organs such as the intestine (calcium absorption), kidney (calcium excretion), bone (calcium storage pool), and mammary gland (calcium secretion into milk and known target organ of prolactin). By then, our animal experiments covered two levels of organization: whole body (calcium balance experiment) and two organ systems (intestine and bone), each was studied at the system level (*in vivo* calcium absorption/bone ^{45}Ca turnover) and organ level (*in situ* perfused intestinal segments/bone in organ bath). For each organ system and each level of organization, not only did the approaches and contents differed, but the methodology also varied widely.

In 2003, my third lucky strike, the Faculty of Science gave permission for the establishment of our **Consortium for Calcium and Bone Research (COCAB)** which came with a big budget for equipments. COCAB was initially made up of basic science researchers and clinical science researchers from Faculty of Science and Faculty of Medicine, Ramathibodi Hospital. We then invited basic and clinical scientists from other universities, who were interested in the same line of research, to join us. The informal atmosphere of our bi-monthly COCAB seminars strengthens our joint research and provides valuable opportunities for cross-disciplinary discussion and exchange of ideas. I must say that institution leaders and policy play an equally big (if not a bigger) role than the granting agency in the advancement of its research.

I was also lucky to have a new research collaborator, Dr. Narattaphol Charoenphandhu a young promising medical doctor with a Ph.D. degree, who joined our department as a full time staff member in 2005. In addition to the two of us, we now have 16 people in the laboratory: 5 Ph.D. students, 6 M.Sc. students, 1 postdoctoral researcher, 2 post-masters researchers and 2 laboratory assistants, one of whom also acts as the laboratory secretary. It is our policy to invite our M.Sc. graduates to stay on for a year or two after graduation (if not already committed elsewhere) as paid research assistants. Of course, most research laboratories wish for postdocs. However, we find our own post-masters to be affordable and are good contributors, as they already have the required background and skills. As a new postgraduate, they are confident and eager to try new techniques and to produce papers for their curriculum vitae.

Having a large number of people working together in a small laboratory can be a headache as well as fun. There are unwritten rules that everyone has to follow, such as no one gets his or her own space or even own seat. Where one works is dictated by the technique or method. Activities are organized to help students to help themselves and their peers. In our laboratory a new student will pair up with a more senior person 'a tutor', who will teach them the basic skills and give advice. This tutorial system is a win-win strategy for everybody; supervisors have more time for other things, senior students learn to share and care, and young students never feel lost and the learning process is accelerated. We encourage discussion among members regardless of research area or status. Students are provided with intensive training and they are expected to meet the high standards of performance.

Group activities (Table 1) are designed for members

Table 1. Group activities as part of graduate training, skill in communications, multidisciplinary approach, knowledge sharing, and teamwork.

Group Activities		Frequency
Journal club		weekly/fortnightly
Lab meeting		weekly
(laboratory report and discussion)		
Mini-seminar	-special techniques	less frequent
	- special topics	less frequent
COCAB meeting		bimonthly
Lunch out or lunch delivery*		
TRF Senior Scholar academic meeting		once a year
Get together party		June & December
(present and former students)		

* to celebrate acceptance of paper, to welcome new member, or to bid farewell, etc.

to learn skills in information gathering, oral communication, creative thinking, reasoning and building comradeship. As the Faculty encourages the practice of knowledge management, we also incorporate knowledge management into the routine work. Besides the tutorial system and sharing of experience and information in various group meetings, we plan to record all protocols used in our laboratory with tips and tricks as video clips and electronic database to be updated by users.

At this time, each research area deals with six levels of organization (Fig. 1). Some new techniques are developed in our laboratory and some are transferred from students who have learned the techniques abroad. It is my luck again to always have team members who are conscientious, responsible, and totally devoted to their work. They have accepted our laboratory policy that their own project is their first priority, but at a certain stage they are expected to contribute their time and skills to another project. By the time students leave, each should have a contribution in at least one paper that is not a part of their dissertation.

Tips for survival

1. Pair up with a colleague or join a research group.
2. Choose a project with a good rationale and clear goal. (analogy of buying a car)
3. Apply for a grant (because, it will force you to stand on our own feet and produce output with dead line)
4. Read and learn about other areas/disciplines (to enable you to cover more levels of organization).
5. Identify the six levels of organization in your work and try to cover more than one level. Go for multidisciplinary research (to add impact).

The present ultimate question is not about survival anymore, but how to make the most of this turn-around. The new generation of integrative physiologists needs to be more versatile, and to develop different skills to go up and down the ladder of organization. This helps to give functional meanings to genes, proteins and cells, all of which add up to a much bigger and more complex sum of higher organisms. In fact, the question should be **"How can Physiology help to bring significance and relevance to modern biology".** That is the present and challenging task of physiologists.

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