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Is Cell and Molecular Biology Divorcing from Clinical Practice?

The stunning success of cell and molecular biology has created 31 Nobel laureates in the last decade, 23 in medicine or physiology and 8 in chemistry. I doubt that any other field of science can claim such an output. This rate of three per year is surely justified because their discoveries hold enormous promise for new therapies. With all of this brilliance, one might think that these discoveries have importantly influenced the practice of medicine. Think again. Of all the Nobel prizes awarded in the past 10 years, only three have affected clinical practice to any extent: the discoveries of prions, nitric oxide, and the polymerase chain reaction. Well perhaps the impact on clinical practice has not been felt yet, but surely clinicians are keeping up with the field in anticipation of a major breakthrough.

Not according to the survey of the American Thoracic Society (ATS) published by Schnapp and coworkers in this issue of *AJRCCM* (pp. 1176-1180). Their online supplement shows that 35% of the ATS membership thinks that *American Journal of Respiratory Cell and Molecular Biology* is not at all valuable (see Table E9A of the online supplement) and that among the services provided by ATS, the Red Journal comes in dead last, with an approval rating of only 2.43 (5 is highest and 1 is lowest) (Table E1B of the online supplement). The *American Journal of Respiratory and Critical Care Medicine* ranks first, with a rating of 4.36, whereas the Red Journal ranks lower than the international conference, ATS policy statements, continuing medical education, online ATS journals, the advocacy/public

policy office, the website, the printed and online rosters, and the ATS News (Table E1B). Does this mean that it publishes bad science or irrelevant articles? Not at all. Although its impact factor is somewhat less than the Blue Journal's 5.96, it is nevertheless a respectable 4.16. Then what does it mean?

Clinicians vastly outnumber researchers in ATS membership by 78 to 22% (1). The Red Journal ranks dead last in ATS services because clinicians outvote researchers, and they are not very interested in cell and molecular biology. They are, however, interested in other types of medical research. Both clinicians and researchers approve the original articles in the Blue Journal, with a rating of 4.09 and 4.32, respectively. In contrast, original articles in the Red Journal are rated 4.11 by investigators but only 2.88 by clinicians. Clinicians deal with diseased organ systems, not individual cells and molecules. Cell and molecular biology does not generally deal with these topics in a way that is helpful to clinicians, whereas the research published in the Blue Journal does.

In contrast with clinicians, the pharmaceutical industry is dependent on cell and molecular biology because they open fabulous new pathways for innovative drug development. The industry pours many millions of dollars a year into its support. Granting agencies the world over, foreseeing spectacular new discoveries, invest billions in this research. Researchers, who follow Sutton's law, become cell and molecular biologists because that is where the money is.

Clinicians probably feel we have gone overboard in support of cell and molecular biology. I agree. With the exception of population studies, it is difficult for medical scientists to obtain support for research that clinicians find informative. Biomedical publications in journals with the highest impact factors, such as *Cell*, *Nature*, and *Science*, deal almost exclusively with cells, molecules, and genes. In this rarified group, only the *New England Journal of Medicine* publishes articles of interest to clinicians. What is worse, impact factors now control academic advancement so that cell and molecular biologists are preferentially promoted within faculties of medicine. Once in positions of power, they are unlikely to relinquish it to other groups. The control of medical faculties by scientists spawned and supported by granting agencies and multinational pharmaceutical companies is a feed-forward mechanism that threatens to maintain their power and to downgrade the importance of clinical practice in medical faculties far into the future.

Obviously clinicians are interested in new drugs, but only when they enter clinical trials, not 12 years previously when the basic research is done. Clinicians, constrained by their patients' problems, and basic medical researchers, lured by the available lucre, are going in different directions. They are already split and appear to be headed toward divorce. Can the marriage be saved? I believe so.

The science of complexity, which seeks to understand emergent phenomena might do the trick. Emergent phenomena arise from interactions of many component parts. They cannot be predicted or understood by studying the parts in isolation. How on earth do the interactions of our neurons ever produce consciousness? The extraordinary appearance of order out of chaos, such as Darwinian evolution and the development of the fetus, appears to violate the second law of thermodynamics. This law, shamefully almost ignored by medicine, states that the universe is becoming steadily more disordered, but living things are highly ordered. How they appear to escape the second law fascinated Claude Bernard (2), but it was a physicist, Ilya Prigogine—the Nobel Laureate—who demonstrated that the spontaneous development of order resulted from driving a system far from thermodynamic equilibrium by making it dissipate energy, for example, by heating it (3).

We all live far from thermodynamic equilibrium by consum-

ing and dissipating energy in a process called metabolism. As a result, we are spontaneously ordered, and the resulting emergent phenomena are what clinicians deal with daily in health and disease. Probably disease results if we move too close to or too far from thermodynamic equilibrium (4). Investigation of our complex physiologic systems has shown that they fluctuate continuously (5–8), and this variability has been called the spice of life (8). Investigation of these phenomena is clinically of broad interest and presents a particular opportunity for respiratory medicine (9). By studying the interactions of integrated systems of molecules, genes, and cells, cell and molecular biologists would conduct research into healthy and unhealthy emergent phenomena that would be highly relevant to medical practice. I hope they do this. It could save the marriage between themselves and clinicians. Divorce is not inevitable.

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The Hormone Replacement Dilemma for the Pulmonologist

Although it has been recognized for years that obstructive sleep apnea (OSA) is more common in men than in women, the impact of menopause on the prevalence of sleep apnea has been less clear (1–3). A number of studies have suggested an increased prevalence in postmenopausal women, but confounding due to age and body mass index have left this issue unresolved (1–3). It has also been proposed that the female hormones, estrogen and progesterone, may modulate apnea pathophysiology and protect premenopausal women, thus explaining the male predominance in this disorder. Although this could also explain the increased prevalence of OSA in postmenopausal women, the administration of estrogen and progesterone to postmenopausal apnea patients has yielded mixed results in terms of improvement in apnea frequency (4–6).

Two papers in this issue of *AJRCCM* (pp. 1181–1185 [7] and 1186–1192 [8]) have brought near closure to several of these issues. First, Young and coworkers (7), utilizing the Wisconsin Sleep Cohort (n = 589), including both longitudinal and cross-

sectional data, have reported a gradual increase in the prevalence of OSA through the perimenopausal period with a substantial increase in postmenopausal women. Their fully adjusted model yielded an odds ratio of 2.59 for OSA (apnea–hypopnea index ≥ 15) in postmenopausal versus premenopausal women. Second, Shahar and coworkers (8), utilizing data from the Sleep Heart Health Study (n = 2,852) observed a 40–50% reduction in OSA prevalence (apnea–hypopnea index ≥ 15) in postmenopausal women receiving hormone replacement therapy (HRT; estrogen or estrogen plus progesterone) when compared with women without such replacement. This was the case after controlling for age, body mass index, and other relevant possible confounders. Of note was the fact that both groups reported a prevalence of OSA (apnea–hypopnea index ≥ 15) in postmenopausal women of 11–12% using a very conservative definition of apneas and hypopneas. Thus, this likely represents real disease.

These observations raise two fundamental questions. By what mechanism does estrogen and progesterone modulate apnea