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COMMENTARY

LYMPHOLOGY, MEDICAL IGNORANCE/IGNORAMICS AND THE NOBEL CONNECTION: Howard Florey, Joshua Lederberg, and Françoise Barre-Sinoussi

M.H. Witte

Department of Surgery, University of Arizona College of Medicine, Tucson, Arizona USA

ABSTRACT

Intriguing interludes with Nobel laureates have marked the history of Lymphology. Bounded (or rather unbounded) by a mutual fascination with ignorance and the unknown, their curiosity converged around microbes, infections, and host responses mediated by the lymphatic system. These studies transcended a simple "molecular model of life."

Keywords: Lymphology, ignorance, ignoramics, Florey, Lederberg, Barre-Sinoussi

With the recent explosion of information in "molecular lymphology" – a diverse array of genes and proteins involved in lymphatic development, growth and function, it is tempting to mold these latest discoveries into a "molecular model of life" (1). Such a premature model, however, would ignore the symmetrically and geometrically expanding domain of ignorance – the "ignorome" – what we know we don't know, don't know we don't know and think we know but don't – surrounding the lymphatic system. The rush to reduce biology and disease to molecules and then adapt informatics to manage the growing information stockpile needs to be balanced by an equally energetic effort in "ignoramics" (2,3). Ignoramics questions dogma, reevaluates neglected insights, identifies key gaps and unknowns, and develops collaborative interdisciplinary approaches to explore complex systems and reconstruct them in diverse environments such as the spectrum of human health and disease. Indeed, even a simplistic "genes to man" concept is already confounded at the molecular level by recent discoveries in epigenomics and differential gene expression patterns in space and time (and in vivo and in vitro), DNA methylation, and the latest, RNA reverse influences on the expression of the DNA code. What greater chasm of the unknown must lie between genotype and phenotype and the promise of personalized genomic medicine.

Lymphology – the discipline – in its science and the journal *Lymphology* in its pages – has especially embraced "medical ignorance" – not as an enemy to stamp out or else to fear or ignore – but rather as an endless frontier to explore, the terrain where all future learning and discovery takes place. This embrace has been a passionate one, accounting for the early pioneers coining the term "lymphomania" and the common use of the "ignorance" term at International Society of Lymphology meetings and in papers appearing in *Lymphology*.

But what about the Nobel connection?

Lord Howard Florey was a lymphologist early in his career – 1920s papers (4) on

intrinsic lymphatic contractility and a 1937 paper (5) on lymphatic proliferation during inflammation (i.e.,"lymphangiogenesis" long before we coined the term in the 1980's and it became a "hot topic" in the late 1990's). And again, following his mid-life interlude with Alexander Fleming launching the antibiotic era with the manufacture of the first naturally occurring antibacterial substance (penicillin) for global use (a contribution that won them the Nobel prize in 1945), Florey returned to the lymphatic system to work with James Gowans on lymphocyte recirculation and trafficking through the lymphatic system. Still later, in the 1960's, he coauthored important papers with two graduate students (both fellow Australians and future card-carrying lymphologists), one a fiery veterinarian-physiologist, Bede Morris (6), who was investigating particulate absorption through the diaphragmatic lymphatics (a process examined with more sophisticated tools in this issue's Liu et al paper (7) and the other, an outspoken young electron microscopist, J.R. Casley-Smith (8), making original observations on the distinctive ultrastructure of lymphatic capillaries. Florey died on February 21, 1968, just a few days before the first issue of the first volume of *Lymphology* was published. Subsequently, those same "Aussie" graduate students with their colleagues and students continued to make seminal contributions in many areas of lymphology. From their writings and presentations and Florey's, each in their own way was fascinated and emboldened by what was not known – the unanswered/unasked questions and unquestioned answers – about the workings of the lymphatic system in health and in disease.

Nobelist Joshua Lederberg, credited by many as a father of molecular biology for his ground-breaking work in bacterial genetics, also wedded a preoccupation with ignorance to a curiosity about lymphology when he contacted me in 2000 with a request "to be so kind as to favor me" with a reprint of an article entitled "Ignorance in infectious disease; the case of AIDS, Kaposi sarcoma, and lymphology" (9), which had appeared a few days earlier in *Lymphology*. He also asked for "more on the Ignorance agenda." Thus began our continuing dialogue (what he termed "broken threads" in the "codification of ignorance") until his death last year. Through letters, e-mails, and exchange of ideas and materials, we discussed how to use ignorance to teach and discover (10). "All this," he wrote, "goes beyond the MD curriculum to the entire system of research". He shared with my Summer Institute on Medical Ignorance high school student researchers/questioners his own personal favorite question – "Are not bacteria cells?" – the simple yet complex question that led to his Nobel prize in 1958 establishing the existence of transduction and translation in bacteria and incidentally providing key tools for the emergence of molecular biology and subsequently, the informatatics-based Human Genome Project. Nonetheless, he continued to question the pre-determinism and reductionism of Watson's DNA helix-code metaphor of life (1).

In 1983, Françoise Barre-Sinoussi, a young virologist working in Paris' Institut Pasteur observed that lymphocytes isolated from the enlarged lymph nodes of a patient with a milder form of a newly described acquired immunodeficiency syndrome were infected with a novel retrovirus resembling the human T-cell leukemia virus HTLV-1. Reverse transcriptase was released into the culture medium as the lymphocytes proliferated, and distinctive serologic responses were noted (11). This lymphadenopathy-associated retrovirus was subsequently renamed HIV and shown to be the cause of AIDS. This year, Barre-Sinoussi shared the Nobel prize for this ground-breaking discovery and her body of work since. Much earlier, in 1987, she participated in the 11th International Congress of Lymphology symposium that brought together experts of the day to Vienna (where Moritz Kaposi, more than a century earlier, described the lymphatic endothelium-

derived sarcoma that bears his name) to examine the known and the unknown (ignorance) about this puzzling epidemic and to explore the relationship of AIDS and Kaposi sarcoma to the lymphatic system's four components and their integrated function. In her contribution (12), subsequently published in a special symposium issue (*Lymphology* 21, 1988, pp 87), her unanswered questions focused on the spectrum of the new virus' cellular tropisms (most researchers were concentrating entirely on the CD4 helper T-cell) and how such studies might uncover unexplained features of AIDS pathogenesis and the molecular mechanisms co-opted by the virus to escape immune system surveillance (that might also serve as therapeutic targets). Over the years since, her research has spanned the spectrum from molecular and evolutionary virology to the immunopathogenesis of AIDS, serologic responses, associated opportunistic infections, targeted therapies, and the epidemiology of the global pandemic. In 1989-1990 and two decades later in 2007-2008, she and her laboratory team mentored two University of Arizona medical student researchers from our Curriculum on Medical Ignorance. The first, Rebecca Greenlee, investigated antibody-dependent cytotoxicity against HIV (13) and subsequently authored a well- cited article on developmental disorders of the lymphatic system (14). Kevin Yarbrough, the second student, has been studying innate immune responses to a novel HIV vaccine (events that intimately involve dendritic cells, afferent lymphatics, and regional lymph nodes). In May 2008, hosted by the Institut Pasteur, he also participated in the 25 year commemoration of the discovery of HIV. He then returned to Arizona to resume his medical studies, full of unanswered questions to pursue long-distance, just before the Nobel selection was announced.

Thus, these three Nobel Laureates – coming from different perspectives, disciplines, and generations – converged their curiosity on the inner workings of microbes and viruses, leading in each case to a profound impact on human health. Whatever the tools of their day – glass cannulae, microscopes, culture plates, or Western blots and microarrays – these were humbly put into the global perspective of the vastness and revolutionary nature of the unknown embodied in their research questions and the wonder that would lie ahead. The timeliness or rather timelessness of their questions is reflected in the urgent global concern now that the pipeline of natural antibiotics, of which penicillin was the prototype, is drying up in part because drug development has focused exclusively on in vitro studies of gene expression associated with microbial virulence while different unexpressed genes are responsible for virulence in vivo through interactions with the host (15), i.e., complex biological interactions overriding narrowly defined DNA sequences. Indeed, the intertwined noble quests of Florey, Lederberg, and Barre-Sinoussi have touched upon and may yet turn on revisiting historical insights and unveiling and mastering ignorance about the biology of the integrated working of the lymphatic system – lymphatics, lymph, lymph nodes and lymphocytes – in health and disease (exemplified in the spread and containment of infectious agents and the host response), i.e., lymphology as defined by the founders of the International Society of Lymphology and chronicled in the pages of *Lymphology*.

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Marlys H. Witte, M.D.
Professor of Surgery and
Director, Student Research Programs
University of Arizona College of Medicine
1501 N. Campbell Avenue, Room 4406
P.O. Box 245200
Tucson, AZ 85724-5200 USA
Tel: (520) 626-6118
Fax: (520) 626-0822
E-mail: lymph@u.arizona.edu