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LYMPHSPIRATION

IGNORANCE IN INFECTIOUS DISEASES: THE CASE OF AIDS, KAPOSI SARCOMA, AND LYMPHOLOGY

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ABSTRACT

From the perspective of The University of Arizona's innovative Curriculum on Medical (and Other) Ignorance focusing on "what we know we don't know, don't know we don't know, and think we know but don't," the shifting terrain of information-knowledge-ignorance of AIDS (a disorder involving, to various incompletely understood degrees, the four components of the lymphatic system–lymph, lymphatics, lymphocytes, and lymph nodes) and Kaposi sarcoma (a lymphedemogenic lesion thought to arise from trans-differentiated lymphatic endothelium) is surveyed by pinpointing some key unanswered questions that have been raised over the course of the epidemic and pointedly in past International Congresses of Lymphology. These questions are placed in the context of general ignorance about infectious diseases and the relationship of "germ" to "terrain" through the "blood-tissue-lymph loop." A framework is suggested for an "ignorance agenda" encompassing basic biology, clinical management, and societal issues.

The Problem and the Challenge

"Just a few years ago in an excess of hubris, I predicted that we were nearly finished with the problem of infection, leaving only a handful of still unsettled matters to be tidied up here and there... I take it back. Legionnaire's disease and Lyme arthritis are only small hints of what might happen, unpredictably, at any time... And now AIDS, only 1200 cases all told, is already causing something akin to panic in New York City, Los Angeles, and San Francisco... We have not run out of adversaries, nor is it likely that we will do so for a long time to come... Whatever we learn about the mechanisms that release Kaposi's sarcoma in AIDS will be useful information for the study of cancer in general, and whatever we can discover about the role of immunity in cancer will turn out to be a piece of applied science for the AIDS problem." Lewis Thomas, 1983 (1)

"The more rapidly knowledge of the disease [AIDS] accumulates, the faster assumptions that seemed solid a year ago begin to crumble. And as solid ground disappears, scientific questions proliferate almost as rapidly as HIV itself. There are thousands of them—in vaccine work, drug research, pathogenesis studies, epidemiology, public health, and molecular biology. There is nothing on the horizon remotely resembling a cure for AIDS. Nor is there anything like a workable vaccine." John Benditt, Science Features Editor, 1993 (2)

"AIDS vaccine development is no further ahead than it was in 1984, when little was known about the epidemic's cause; we have no guarantee that we will ever have a vaccine." Robert Gallo, 1998 (3)

"In any era in the long history of medicine most of the ideas about etiology and therapy are either flagrantly wrong or superseded by better ideas." Alvan Feinstein (4)

"Is it credible that such a mushroom of knowledge [science of the day], such a growth overnight as this, can represent more than the minutest glimpse of what the universe will really prove to be when adequately understood? No! Our science is a drop, our ignorance a sea." Philosopher William James (5)

"The greatest single achievement in this most scientifically productive of centuries is the discovery that we are profoundly ignorant. We know very little about nature and we understand even less. I wish there were some formal courses in medical school on medical ignorance, textbooks as well, although they would have to be very heavy volumes." Lewis Thomas (6)

The late renowned physician essayist Lewis Thomas, once optimistic about the eradication of infectious diseases by public health measures and antimicrobials, later reevaluated this optimism as he witnessed the emergence and reemergence of a variety of infectious diseases and the unfolding of the epidemic of acquired immunodeficiency syndrome (AIDS) (7). During acceptance of the Kober medal from the American Association of Physicians in 1983, he expressed surprise at receiving the honor because he had never really answered any of his basic questions about infectious and autoimmune diseases and confessed that even the Schwartzmann reaction and bacterial endotoxins, which had launched his research career, were still a biologic mystery to him "nowhere near control much less understanding" (8).

In the context of medical ignorance—and the long unknown distance we must admit to before we can begin to travel, this article highlights some of the ignorance that pertains to infectious diseases specifically focusing on the global epidemic of AIDS, the event that Generation Xers (age 18-29) have identified in a recent survey as their defining event—the most central to their experience and age (9). We also consider briefly the once rare "idiopathic multiple pigmented sarcoma of Kaposi" (Kaposi sarcoma) (KS), now thought to be an infectious process, in a similar light along with a sampling of other known or putative infectious disorders. Our aim, using infections as an example, is to develop several unifying themes about lymphology and more generally about learning, science, and discovery that may be freshly approached through the Curriculum on Medical Ignorance inspired by Lewis Thomas (viz. 6). Indeed, many of these fundamental questions have puzzled scientists and physicians for centuries and relate to properties attributable to the infectious agents themselves ("virulence") or to the nature of the host response ("resistance"), both closely intertwined with the lymphatic system. To these must also be added the influence of deliberate external interventions such as medications and public health measures, the societal context in which both infection and scientific investigation take place, and the coloring of interpretations of "knowledge" by emerging theories of chaos and complexity.

Nineteen years have passed since the first case reports of AIDS (originally termed GRIDS—gay related immunodeficiency syndrome) were simultaneously described on the East and West coasts of the United States. By 1998 (the latest detailed WHO report), approximately 420,000 had died of AIDS in North America and 11.7 million globally; an estimated 860,000 were living with human immunodeficiency virus (HIV)/AIDS in North America and 30.6 million worldwide, 5.8 million having acquired the infection in the past year; and 8.2 million children less than age 14 had been orphaned since the epidemic began (10). And the pandemic continues to spread relentlessly. Despite an explosion of knowledge about the syndrome and the epidemic (the putative causative human immunodeficiency virus, HIV, and other AIDS-associated "opportunistic" microorganisms, details of the host

immune response in HIV infection and AIDS, and a therapeutic arsenal of antiretroviral and chemoprophylactic drugs reputed to have lowered the death rate and converted AIDS into a chronic illness in the United States), unanswered questions persist and proliferate. Each answer, each trumpeted breakthrough, seems to generate new and ever more troubling questions. Many of these perplexing questions were formulated early in the epidemic, and some were once thought to be largely answered but the answers found later to be incorrect or incomplete. Many others are yet to be explored, and an unknown number haven't even been formulated. These questions range from the origin of the epidemic—when, where and how; distinctive properties of the causative virus (perhaps even viruses) and coinfecting microorganisms; unpredictable sequence of host responses and even the spectrum of cell types involved; appropriateness of surrogate markers of disease progression; expected outcomes with and without intervention; rationale, effectiveness, cost, and accessibility of current treatment regimens; sound prophylaxis and practical preventive measures including "safe sex" and vaccines. Whereas many of these questions have been cast in the framework of ongoing research and "uncertainty," the history of AIDS, its high mortality and morbidity and relentless spread globally in the face of burgeoning information, promising leads, false hopes, and public mood swings, suggest that a more appropriate term is "ignorance" and even "ignore-ance (11)" which envelop this entity in its urgent social context . "Ignoreance" is denial/neglect/or obstruction of what is or could be known and put into practice, for example, as Peter Piot stressed at the end of the 12th International AIDS Conference in July 1998, "The biggest AIDS gap of all is the gap between what we know we can do today and what we're actually doing" (12). Most of the fundamental key unanswered questions are common to all infectious diseases, and many apply to medicine, science, and knowledge in general.

To bring the subject "out of the closet," the Curriculum on Medical Ignorance (CMI) at The University of Arizona focuses on how to recognize and deal with ignorance through questions, questioning and questioners (Q3 or the 3Qs c.f. 3 Rs) and then applies this "knowledge" and set of skills, attitudes, and behaviors to medical (and other) topics in a variety of formats (13-16). In this essay, we provide a brief background on CMI and then attempt to "diagnose" and "treat" ignorance surrounding AIDS, KS, and other infections from this perspective by surveying persistent and newly recognized unknowns (questions). The point to be made is that CMI's lessons would promote a more forthright, inclusive, and broadly based formulation, create a fruitful open forum to pursue questions, many of which relate to the lymphatic system, particularly the increasingly neglected "big important questions" (BIQS) (17). Understanding and management of these disorders would thereby be enhanced while stimulating translation of advances from the test tube/culture plate/experimental model in the laboratory to the sick patient's bedside.

Curriculum on Medical (And Other) Ignorance: Exploring the Terrain of Learning and Discovery

"Knowledge is like a sphere, the greater its volume, the larger its contact with the unknown." Mathematician Blaise Pascal (18)

"When we consider the reasons we have to think that what lies within our ken is but a small part of the universe, we shall discover an huge abyss of ignorance." John Locke (19)

"Science is the topography of ignorance." Oliver Wendell Holmes (19)

"Knowledge is the raw material of ignorance and vice versa." Marlys Witte (19)

"If we set out to give as little help as possible to originality in science, we could scarcely devise a better plan than our educational system. Youngsters ought to be told what is unknown about ourselves and our universe as well as what is known." Nobel Laureate William N. Lipscomb (19)

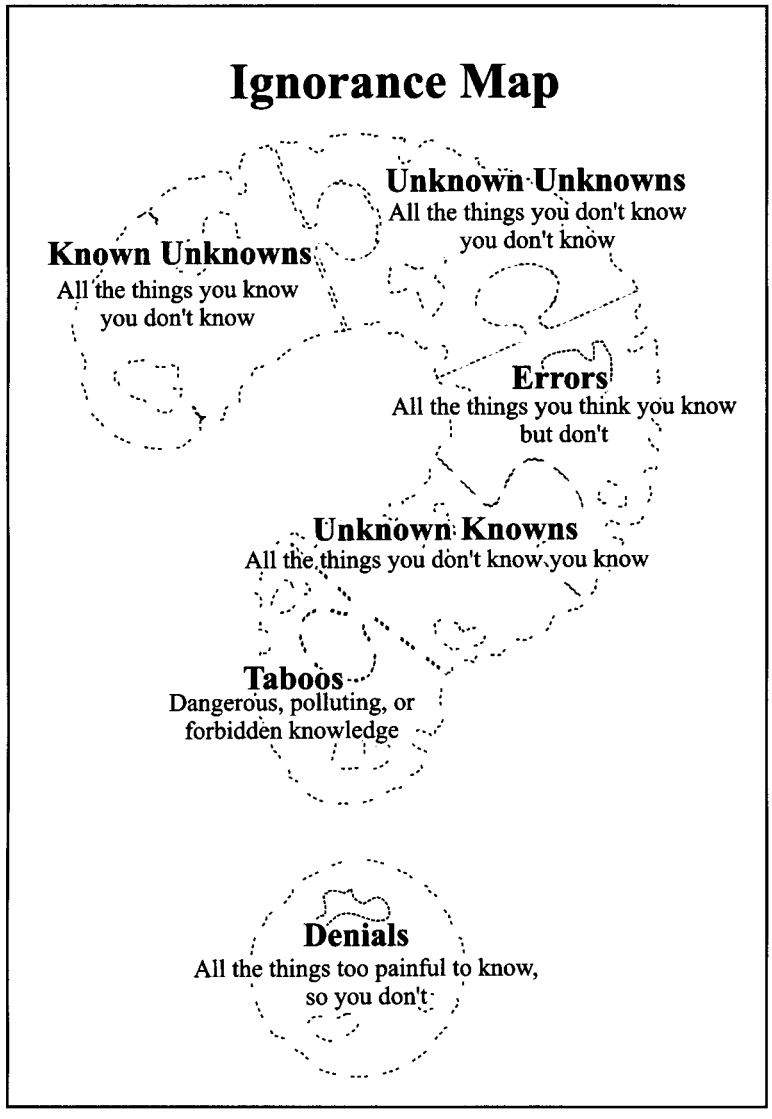

Fig. 1. The Ignorance Map is composed of six major terrains and provides a continu-ously shifting template for forays into ignorance and the unknown on any topic. (Reproduced with permission, 15).

"Our students should be freed from the stupefying excess of fact engorgement, which threatens to convert them into floppy disks encoded for our present ignorance." Lloyd Smith, former University of California in San Francisco Medical Dean (20)

"Scepticemia: an uncommon generalized disorder of low infectivity. Medical school education is likely to confer life-long immu-nity." Petr Skrabanek, PJ McCormick (21)

"And just maybe a new set of courses dealing systematically with ignorance and science might take hold. The scientist might discover in it a new and subversive technique for catching the attention of students driven by curiosity, delighted and surprised to learn that science is exactly as [Vannevar] Bush described it: an 'endless frontier'. The

humanists for their part might take considerable satisfaction in watching their scientific colleagues confess openly to not knowing everything about everything... It is worth a try." Lewis Thomas (22)

Lewis Thomas' novel proposal for a Curriculum on Medical Ignorance (vide supra) struck a responsive chord in us, and in 1984, we decided that this whimsical prescription proposed by our New York University School of Medicine teacher and mentor deserved a try. A healthy dose of ignorance might just be what is needed to revive ailing medical education, which too often stresses rote memorization of facts and lockstep progression and promulgates hierarchal pronouncements. Contemplating solid organ tumors such as cancer of the breast, rectum, and pancreas, enigmatic inflammatory bowel diseases such as Crohn ileocolitis, the then new epidemic of AIDS, and innumerable other poorly understood human afflictions, we speculated that a frank admission of ignorance or even insertion of a few blank pages to introduce a textbook chapter on egregiously vexing disorders would more accurately highlight limited understanding and inability to prevent or arrest these particular disease processes. This conspicuous gap (viz. blank pages) in an authoritative textbook might even stimulate youthful and still impressionable minds to pursue new pathways of investigation out of the mainstream. After all, even artificial hearts and organ transplants—miracles of modern surgery—attest to a fundamental ignorance about progressive cardiac, renal, hepatic, and pancreatic dysfunction. Only at the most advanced stages of disease or in despair over the inadequacy of current treatment regimens are these highly technological procedures offered to resuscitate life. Indeed, the discipline of Surgery itself—removal of organs and dissection of the living body—is the ultimate but still necessary biologic exercise in ignorance. As the preeminent surgeon John Hunter recognized several centuries ago, *"It (operation) is like an armed savage who attempts to get that by force which a civilized man would get by stratagem"* (22). Furthermore, as information and knowledge march forward, so too does the ever enlarging body of ignorance. Thus, knowing and not knowing, as William James and Blaise Pascal recognized (see citations 5,18 earlier) are inextricably intertwined and symbiotic.

At least six lands or terrains lie within the domain of ignorance (*Fig. 1*, Ignorance Map) (15,16): all the things we know we don't know (known unknowns); all the things we don't know we don't know (unknown unknowns); all the things we think we know but don't (error); all the things we don't know we know (tacit knowing, intuition); taboo (forbidden knowledge) (23); and denial.

As chemist Henry Bauer points out (24), there are varying degrees of probability and certainties that change with time as we move from word of mouth to what is contained in textbooks. In other words, the Ignorance Map *(Fig. 1)* is in a constant state of flux with shifting and permeable boundaries. Closely linked to the ignorance paradigm are the evolving concepts of chaos/complexity, fuzzy sets, and failure theory (25-29). Whereas The Wall Street Journal (30) welcomes this coming Age of Ignorance in the 21st century as a time of opportunity, the greatest scientists are already supremely comfortable in this world:

"You see, one thing is, I can live with doubt and uncertainty and not knowing. I have approximate answers and possible beliefs and different degrees of certainty about different things ... I don't feel frightened by not knowing things." Nobel Laureate physicist Richard Feynman (31)

The core content, the "what" of CMI, is the terrain of ignorance. In any discipline or for any individual, this core consists of the unanswered, wrongly answered, neglected, avoided, and yet to be formulated questions—the terra incognita of all future learning and discovery. How does one "teach" ignorance, i.e., impart the knowledge, skills, behaviors, and attitudes to recognize and deal with the

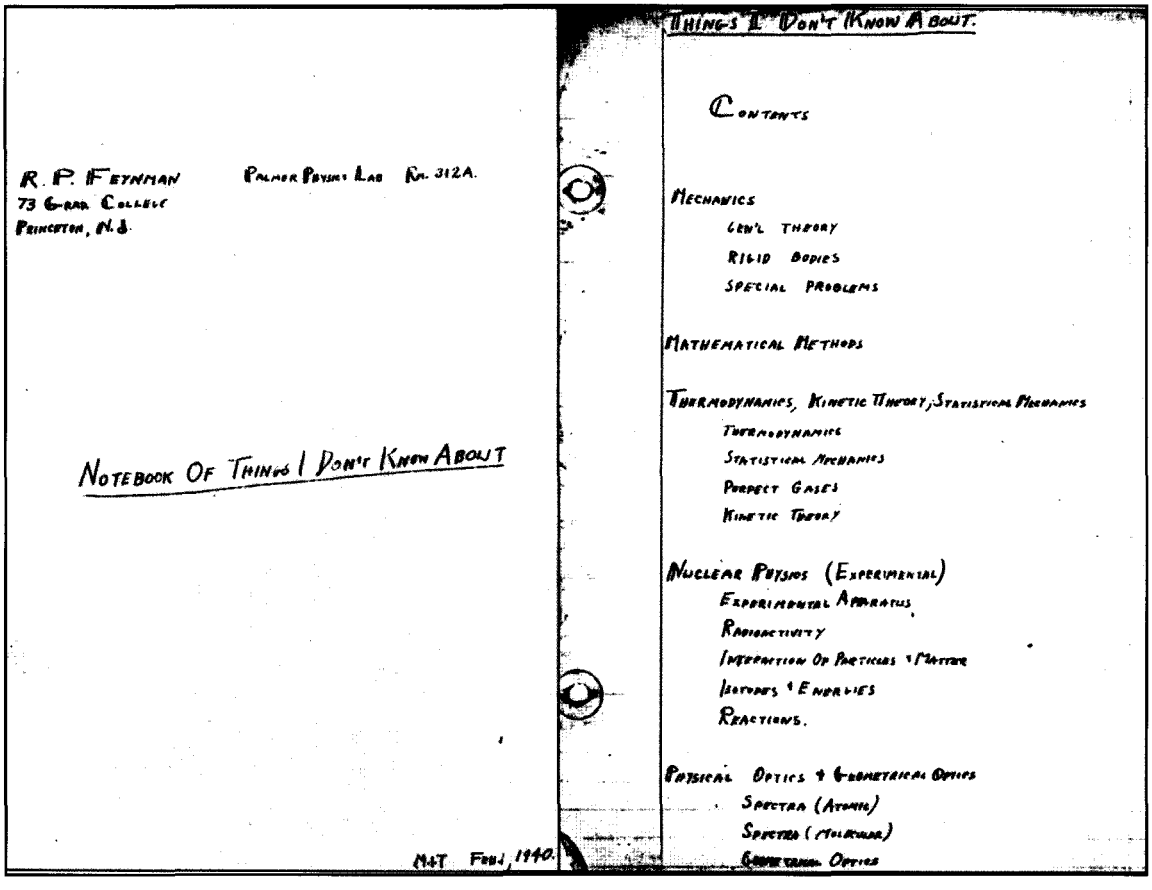

Fig. 2. Nobel laureate physicist Richard Feynman's "Notebook of Things I Don't Know About" which resembles a CMI Ignorance Log (Reproduced with permission) (34).

3Qs or Q3 (questions, questioning, and questioners)? To facilitate the uncorking of questions (the "how" of CMI—practicing the questioning process), as many questions as possible are elicited in a delimited time from the student/learner (questioner) regarding a series of specific medical topics (e.g., AIDS, KS, breast cancer or artificial hearts). Only after inhibitions about asking questions are released can a meaningful dialogue begin between student and teacher-investigator (ideally, also a lifelong student). Using three categories of questions that generate a broad picture and avoid the pitfalls of neglecting major areas, fundamental questions are listed about basic biology (Type 1 questions), clinical or practical questions about management of a specific patient or groups of patients and their medical problems (Type 2 questions), and questions that go beyond individual patients and deal with complicating and overriding societal, economic, legal and ethical issues (Type 3 questions). Most importantly, whether in the classroom, laboratory, or clinic, the primary focus is on the student's (learner's) unanswered questions rather than the teacher's programmed questions. The latter represent the usual substrate of small group interactive sessions and "hands-on" laboratory exercises which get beyond the traditional didactic lecture. CMI goes further by assuring that the exercise from the outset is maximally "brain-on" from the learner's perspective.

Of particular relevance for this learning experience is the Ignorance Log on which students record their questions on a specific research or disease topic as well as more general ponderings. These questions are followed serially (e.g., weekly) and also charted on progressive Ignorance Maps *(Fig. 1)*. Analogous formats have been a routine exercise for many great thinkers such as Nobelist Feynman's "Notebook of Things I Don't Know About" (34) *(Fig. 2)* or the Cahier Rouge of renowned French physiologist Claude Bernard (35). Serial Ignorance Logs and Ignorance Maps chart, dissect, and categorize the shifting terrain of ignorance and provide the framework for a succinct final Ignorance Report (a term paper limited to 4 double-spaced pages). The latter, e.g. on AIDS, KS, or a potpourri of other topics, encompasses the student's beginning questions, those answered, those found in retrospect to be most important and fruitful, and new questions discovered in library computer searches/laboratory or clinical research and in interviews with experts (ending questions). Course grades depend on progress of the questioning process to reach the "cutting edge" rather than on the often quick or superficial intermediate answers found along the way during and implicit in this process. In addition, ignorance-based Ward Rounds, Departmental and Grand Rounds including Morbidity and Mortality conferences (perhaps better termed "Failure Rounds"), and Ignorance Clinical Pathologic Conferences (CPCs) focus on what is left unknown and unanswered about the patient(s), topic, or field when the student (professor or practicing physician) leaves the conference room, clinic, laboratory, autopsy table, or completes the final pathologic examination. Questions also include those posed by the patient/family and still unanswered. Whereas International Conferences on Medical Ignorance have brought together world-recognized experts renowned for their knowledge, these same individuals have also been attuned to what is missing, unknown, unclear, and possibly wrong, i.e., the ignorance surrounding and at the cutting edge of their discipline.

Other components of CMI *(Table 1)* include "distinguished visiting ignorami," "Visiting Professors of Medical Ignorance," who highlight in one lecture or traditional seminar what they know (or at least think they know) and in a second informal autobiographical confessional (at times set in La Residencia del Incógnito—the House of Ignorance—a designated bookless paperless-slideless space committed to exploring ignorance and resonating with Amman's 1998 "don't touch this" slideless think tank AIDS workshop) (36), all that they don't know (BIQs) in their area of expertise. When this type of activity is organized into a teaching, clinical, or research conference, the focus turns to unanswered questions, discoveries, pinpointing of ignorance, and subsequently to ways to prioritize and pursue these Type 1-3 questions. Where medical decisions are mandatory, e.g., for example when life hangs in the balance, a rational course of action must be undertaken swiftly despite real but unavoidable ignorance about many aspects of the disease process and the patient. It is important to point out that early on, emphasis is on the number and variety of the student-learner's questions rather than on designating the one or two "best" questions and how only those might be pursued in a reductionist fashion in a controlled research setting. That is, a conscious attempt is made to guide the student towards raising big important questions (BIQs) and learning how to explore them, something we will return to later. At The University of Arizona, we are often most proud of those students who graduate more (knowingly) ignorant than when they entered. For a fuller discussion of these and other CMI components including evaluation tools, see references 13-16.

AIDS and Ignorance

"It's the virus, stupid." David Ho (37)

TABLE 1
Goals and Activities of the Curriculum on Medical and Other Ignorance

Curriculum Goals	Activities
Gain understanding of the shifting domains of ignorance, uncertainty and the unknown: philosophical and psychological foundations and approaches to learning, questioning, and creating "knowledge"; history and development of selected ideas and methods in basic and clinical medical science; mastery by in-depth multidimensional exploration of selected timely medical topics. Improve skills to recognize and deal productively with ignorance, uncertainty, and the unknown: questioning critically and creatively focusing on raising, listening to, analyzing, prioritizing, and answering questions from different points of view; communicating clearly in different media with various audiences; collaborating effectively with different people and other resources. Reinforce positive attitudes and values of curiosity, optimism, humility, self-confidence, and skepticism.	Summer Institute on Medical Ignorance Full-time basic and clinical research Seminars and Clinics on Medical Ignorance Freshman Colloquium on Introduction to Medical and Other Ignorance Questions, Questioning, Questioners (Q^3)Project Creative Thinking Exercises Final Oral and Written Ignorance Reports Weekly Ignorance Logs Sequential Ignorance Maps Ignorance Field Trips Pondering Founds Failure Rounds Ignorance Ward, Departmental, and Grand Rounds Ignorance Conferences Visiting Professors of Medical Ignorance *La Residencia del Incógnito*

"Le germe n'est rien: c'est le terrain qui est tout." (The germ is nothing, the terrain is everything.) Louis Pasteur (38)

"I feel sorry that Nature has not done more to give his (Duesberg's) view prominence. It would have hastened the process by which the scientific community is coming around to the view that the pathogenesis of AIDS is more complicated than the baby talk stories we were all given a few years ago." John Maddox, NATURE Editor, 1991 (39)

"The more we learn [about AIDS] the less certain we are." Jon Cohen, SCIENCE, 1993 (40)

"After l5 years of horror, denial and despair, science may finally be turning the tide on AIDS... providing hope with an asterisk... The most important fact about AIDS: it is not invincible." TIME, 1997 (41)

"AIDS drug cocktails since l996 cause steep drop in deaths." Wall Street Journal, 1998 (42)

"Optimism about AIDS is premature." T. Philipson and R. Posner, Wall Street Journal, 1998 (43)

"Treat early, treat hard, treat smart." R. Gulick, JAMA, 1998 (44)

"'Protease-sparing' vs. 'Hit early/hit hard' : is it better to fire all of your guns at once or to save your best for last?" Hepatitis Weekly, 1998 (45)

"International AIDS meeting injects a dose of realism [compared with upbeat mood of 2 years ago]." SCIENCE, 1998 (46)

"Geneva brings AIDS reality check." American Medical News, 1998 (47)

"Doomsday scenarios, naysayers, dire predictions, scare stories hurt AIDS research." David Ho, 1998 (48)

"AIDS running wild... rivals Black Death of Middle Ages and influenza pandemic of 1918-1919 as global horror." International Herald Tribune, 1998 (49)

"In 1996, a scientist claimed to have found a way to defeat AIDS. On the wave of eupho-

TABLE 2
AIDS QUESTIONS 1987-1991

1987-1988	1989-1990	1991
❑ Are regional and central lymph HIV positive more so than blood? Lymphogenous vs. hematogenous HIV spread? Which cells mediate spread? What determines lymph node effects—protective, predictive, propagative?	❑ Which effect/infection comes first and is most important: CD4↓, CD8↑ involvement of antigen-presenting cells/vascular endothelium/bone marrow cells, B cells, hypergamma globuinemia?	❑ CD8 compensatory response protective?
❑ What determines HIV productive expression in a given cell and which cells participate and how?	❑ Role of cell shape responses/ responsiveness?	❑ HIV kills or exhausts CD4?
❑ Relative importance of free and cell bound virus and viral protein?	❑ Nature of immunodeficiency/ dysregulation humoral cellular?	❑ HIV necessary and sufficient? What are AIDS cofactors? Koch's postulates fulfilled, relevant?
❑ Role of autoimmunity and of dysregulation of angiogenesis in pathogenesis?	❑ Should AIDS stand for acquired immunodysregulation rather than immunodeficiency syndrome?	❑ Role of autoimmunity?
❑ Genetic host/viral factors in disease susceptibility/progression?	❑ Immunologic compensatory mechanisms?	❑ Why immunity variable and generally not protective?
❑ Will antiviral/vaccine therapy work in vivo in large populations?	❑ Relative importance and timing of CD4 destruction, altered lifespan, trafficking, and regeneration abnormalities?	❑ HIV increases virulence of opportunistic invaders?
❑ Pros and cons of mandatory HIV testing?	❑ HIV regulatory gene products involved in neoplasia; heterogeneity; definable components of immunosuppression/ stimulation?	❑ How does HIV infection progress/transmit?
	❑ Best prognosticator, predictor of progression?	❑ If HIV doesn't kill CD4, what is a rational therapy?
	❑ Why latent infection becomes immunodeficiency?	❑ Why not restore immune function by treatment with RE stimulants and immunopotentiator drugs?
	❑ Other occult retroviral infections?	❑ What are the difficulties with vaccine development; can they be overcome?
	❑ Treatment by immunologic compensation? How?	

ria that followed, a batch of new drugs flooded the market. Four years later, those drugs are wreaking unimaginable horrors on the patients who dared to hope. What went wrong?" Celia Farber, Gear Magazine, 2000 (50)

"AIDS and HIV have spurred the most concentrated program of biomedical research in history, yet they still defy our counter-attacks. And our focus on extirpating the virus may have deflected less ambitious, though more pragmatic, aims, including learning to live with the virus by nurturing in equal measure the immune system that HIV erodes. After all, natural history points to analogous infections in simians that have long since achieved a mutually tolerable state of equilibrium." Nobelist Joshua Lederberg, Science, 2000 (51)

TABLE 3
TOP UNANSWERED QUESTIONS PROVIDED BY AIDS EXPERTS IN SCIENCE 1993 SURVEY (39)

TOP 10 QUESTIONS ABOUT AN AIDS CURE	TOP 10 QUESTIONS ABOUT AN AIDS VACCINE
❑ What causes the immune system collapse seen in AIDS	❑ What are the correlates of human protection?
❑ How can HIV replication be controlled?	❑ How can viral variation be overcome?
❑ What are the correlates of protection?	❑ What is the best way to present viral antigens to the immune system?
❑ Can combination therapy overcome drug resistance?	❑ What are the key viral antigens that confer protection?
❑ What are the best targets in the viral life cycle for therapy?	❑ Are "old fashioned" attenuated and killed virus approaches better?
❑ Will immunotherapies like vaccines and cytokine treatments work?	❑ How is HIV transmitted sexually, maternally, and intravenously?
❑ Can drugs target HIV in reservoirs like the lymph nodes?	❑ Is mucosal immunity critical to preventing infection?
❑ How is HIV transmitted sexually, maternally, and intravenously?	❑ What is the pathogenesis of HIV?
❑ Can the immune system be reconstituted after infection?	❑ Should AIDS vaccines aim to prevent infection or disease?
❑ What are the best surrogate markers for evaluating therapies?	❑ Can better animal models be developed?

AIDS has been a popular topic since the first CMI classes were organized at The University of Arizona. Medical students have chosen AIDS as the subject of their Final Ignorance Reports since 1985; since 1995, undergraduate college students in the Freshman Colloquium: Introduction to Medical (and Other) Ignorance, have also delved into AIDS from this perspective, articulating their beginning, ongoing, and lingering questions after researching the topic and interviewing experts (52). Among the questions articulated by the first group of CMI students in 1985 were: When did AIDS first appear? Is HTLV-III [the subsequent HIV] not only necessary but is it a sufficient cause of AIDS [and are there perhaps more important co-infecting viruses (e.g., the latest is HHV6)]? What are the ramifications of HIV serologic testing? Are patients better off with treatment, and what type of treatment? What accounts for the profound immunodeficiency in AIDS? [How many of these questions are satisfactorily answered even today?] Beginning in 1987 in Vienna (53) and again in 1989 in Tokyo (54), 1991 in Paris, 1993 in Washington, DC, 1995 in Sao Paulo, 1997 in Madrid, 1999 in Madras (Chennai) (the epicenter of the burgeoning epidemic in India), and scheduled for 2001 in Genoa, AIDS workshops have been organized around the theme of medical ignorance (the "known and the unknown") under the aegis of the biennial International Society of Lymphology (ISL) worldwide Congresses *(Table 2)*. These seminars highlighted experts' unanswered questions on AIDS and KS as disorders of the lymphatic system and its four components—lymphatics, lymph, lymphocytes, and lymph nodes. Also, a 1989 American Association of

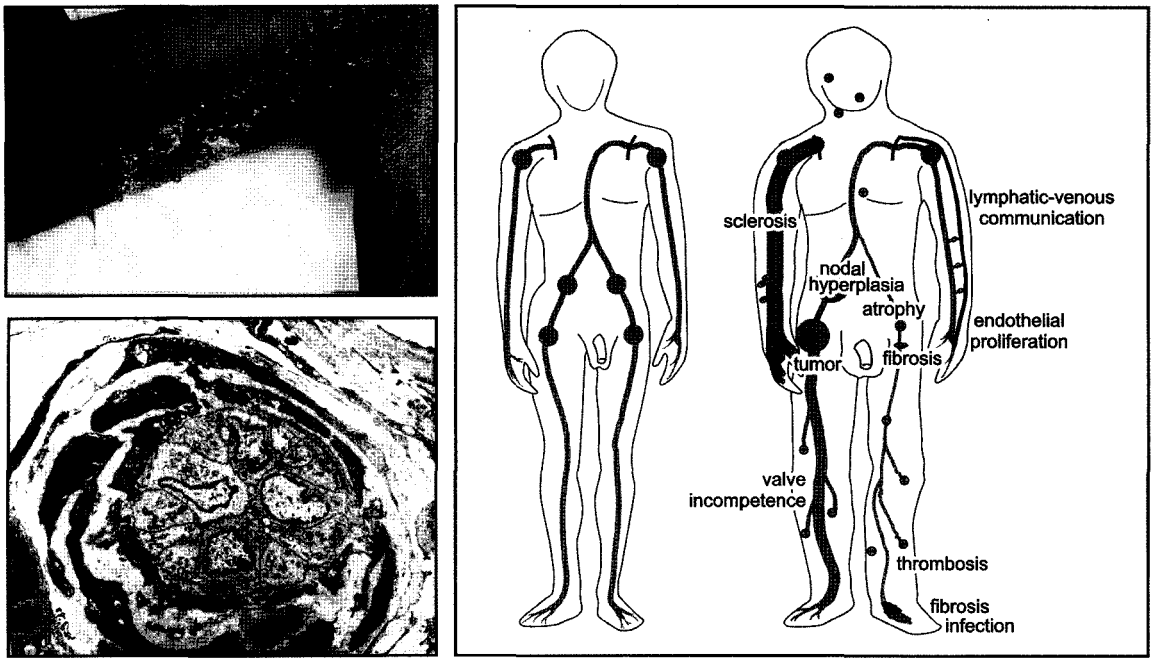

Fig. 3. Pathophysiologic processes in KS closely linked to the lymphatic vascular system. Left upper: African KS where lymphangiomatoid skin lesions of the leg follow the course of the peripheral lymphatic system (courtesy, Dr. R. Dorfman); Left lower: electron photomicrograph showing proliferating endothelium occluding the microvascular lumen in skin of a patient with AIDS-associated KS and lymphedema. Right, schematic drawings of lymphatic images obtained by radiotracer lymphangioscintigraphy (LAS), showing normal pattern (left) and the spectrum of pathologic changes in KS based on LAS findings (see also Fig. 4).

Physicians (Western section) plenary lecture recounted a personal odyssey in medical ignorance and illustrated how the exploration of individual patients embodied the principles of CMI (55). In 1991, AIDS was also prominently featured at The University of Arizona's First International Conference on Medical Ignorance in Tucson, CMI components extensively described, and a keynote lecture presented by philosopher Dennis Rohatyn on the "germ theory of medical ignorance" (56). In 1993, for the first time in the twelve years since the epidemic began, leading AIDS researchers (74 surveyed) publicly acknowledged and reflected on key "unanswered questions in AIDS" (i.e., known unknowns) in a cover-featured article in Science focusing on the search for a cure and a vaccine (39,57) *(Table 3)*. Particularly since 1993, many scattered news stories have highlighted key unanswered questions at open as well as exclusive international conferences and workshops, most notably and extensively at the 12th (1998, Geneva) and subsequent International Congresses on AIDS.

The roller coaster mood swings of the scientific community and the public at large during the unfolding of the AIDS pandemic (from pessimism and depression to optimism and euphoria and back again to a new "realism") actually reflect repeated cycles of questions, tentative answers, and more questions surrounded by taboos, denials, fear, and uncertainty. The Journal of the American Medical Association has appropriately presented two single issue blank, empty AIDS commemorative covers in July 1996 and July 1998 (58) to draw attention to "what might have been" (the potential contributions of those who died in their prime) and "how

TABLE 4
AIDS QUESTIONS FROM SURVEY OF IGNORANCE EXPERTS 1997-1999

TYPE 1–Basic Biology

❑ Viral and host genetic determinants for disease progression? Correlates of immune protection? Mechanisms in CD4 cell loss? Abnormal regeneration of CD4s in HIV infection? Impact of HIV-1 diversity on transmissibility, virulence and immunogenicity?

❑ Is HIV necessary and sufficient to cause disease? Other cofactors in pathogenesis? If such high HIV derived RNA in plasma viral load, why so difficult to culture virus?

❑ Precise mechanisms of HIV pathogenesis? HIV as cytopathic in vivo as in vitro? How much immune system damage attributable to integration of HIV DNA into critical genes regulating immune function? Lifetime of a lymphocyte bearing such HIV DNA integrated genes and giving rise to progenitors with these defects? Which CD4 subsets impacted by HIV? Ho-Shaw rapid production model apply to these subsets or even correct?

❑ Role of autoimmune reactions common to retroviral infections in AIDS pathogenesis?

❑ When and where did AIDS really begin? How long has HIV been around?

❑ Which other viral proteases inhibited by anti-HIV protease inhibitors?

❑ How can these genomically insignificant viruses cause such biologic chaos and how do these chronic bacteria, viruses, etc. act over such long periods of time?

❑ Critical HIV-1 antigenic determinants for protective immunity among variant isolates?

❑ Viral features susceptible to host immune surveillance?

❑ Protective epitopes and protective components of humoral/cellular immunity against myriad different viral strains?

❑ Regarding antiretrovirals, how does virus longevity interface with cell longevity and virus continually spread into susceptible host cells when replication level is nearly zero? How make "sequestered" virus, e.g. lymphoid tissue, susceptible to antiretrovirals?

❑ Functional determinants in mononuclear phagocytes and HIV effects, e.g. pulmonary macrophages, microglia?

❑ True seroreversions characterized by loss of HIV seropositivity and long term survival have been documented in both infants and adults. What processes are at work and what do they tell us about how to cure AIDS?

❑ Where does lymphocyte turnover take place in adults and by what mechanisms? Is there increased killing of CD4?

TYPE 2–Clinical Management

❑ Combine anti-retroviral therapies and immune therapy and what is best immunotherapy in such case? Vaccines work and how to stop viral escape?

❑ Can low doses of Th1 cytokines or synthetic peptides effecting Th1 activity level restore substantial protective T-cell function? Can anti-HIV antibodies from novel sources directly or by molecular engineering provide broad spectrum antibodies for passive therapy?

❑ If anti-HIV protease inhibitors were used in rheumatoid arthritis, systemic lupus erytematosus or fibromyalgia, what would happen?

❑ How many (?all) chronic "auto-immune," "oncologic," "idiopathic" diseases are caused by an infectious agent (e.g., Lyme arthritis, duodenal ulcer, cervical cancer)?

❑ How get compliance over years on complex and toxic therapeutic regimens that are difficult to take?

❑ What explains long term survivors treated by antiretroviral drugs, i.e., which nutritional, stress-control, risk-elimination (e.g., getting off drugs and avoiding repeat STDs), or folk remedies are beneficial alone or combined?

❑ Is CD4 cell turnover increased in AIDS and is that fundamental or incident to the pathology?

TYPE 3–Societal Issues

❑ How many would be dead of HIV if the first cohort with KS had been quarantined for life?

❑ Can we ethically subject human volunteers or HIV positive to in vivo administration of tracers such as bromouridine and cell-tracking dyes and/or biopsy to discover patterns of cell turnover? What level of invasive measurement is acceptable?

❑ When will appropriate priority be given to prevention rather than treatment?

❑ How change attitudes and sexual habits in newly emerging HIV epidemic with young gay men, indigent IV drug abusers, and heterosexuals?

❑ Why develop anti-AIDS treatments that cost tens of thousands of dollars per year per patient when vast numbers in US and globally can't afford them? Why not limit search for economically viable new therapies?

much there is yet to do" (both are terrains of ignorance and the unknown). Experts are once again since 1998 expressing the view that the pathogenesis of AIDS is more complicated than they once thought; they are not so optimistic as they were about treatment in 1996 when protease inhibitors and viral load monitoring were hailed as unconditional breakthroughs on the verge of possible cures. Problems with antiviral drugs including non-compliance, prohibitive expense, drug resistance, drug toxicities [such

as cardiovascular complications and "protease paunch" (59) possibly linked to more general effects of protease inhibition on metabolic processes] and setbacks in vaccine trials probably signify that the best hope against the epidemic is prevention, the same crucial strategy since it began. But prevention is not being pursued as vigorously as it could and should—globally or even in the United States [see Piot quote (12)]. Nor is adequate attention being paid to immunorestoration, which according to Nobelist Joshua Lederberg still holds the greatest therapeutic promise (vide supra, ref. 51). Complex societal issues that range from economic disparities and legal ramifications to sexual taboos and escalation of the profit motive in drug development and the biotechnology enterprise further cloud the picture. It is also unclear how best to set priorities and the public mood to advance the research-action agenda.

In connection with this article, we conducted a survey of a cadre of select "experts" on AIDS and ignorance (distinguished "AIDS ignorami") (see ACKNOWLEDGMENTS). They were asked to list their most important Type 1 (basic biology), Type 2 (clinical), and Type 3 (societal) questions related to AIDS, KS, and infections in general. Sequential collections of key unanswered questions (1987-1999) are summarized in *Tables 2-4* including *Table 3*, a listing of the survey responses highlighted in Science in 1993 (39). One should note the recurring nature of many of these questions since the beginning of the epidemic as well as the failure to address many adequately, such as diverse immunorestorative treatment approaches, the participation of AIDS cofactors (non-HIV), and outcome measures, a shortcoming emphatically driven home at recent International AIDS conferences. These questions fall into both ignorance and "ignore-ance" (11) categories. Whereas most listed are "known unknowns" (although some experts may regard a few as knowns), a clear designation of the five other lands of ignorance on the Ignorance Map (Fig. 1) (unknown unknowns, errors, tacit knowing, taboos, and denials), has not yet taken place despite strong relevance to appreciating the breadth, depth, and persistence of ignorance surrounding AIDS and thereby hindering future progress in finding answers.

Kaposi Sarcoma and Ignorance

An infectious etiology has been proposed for Kaposi sarcoma almost since the original description of this puzzling disorder in 1875. Cytomegalovirus, Epstein-Barr virus, papilloma viruses, and even HIV itself have been recent suspects with homosexual transmission among men considered an important mode of spread. But it was not until 1995 that a highly specific association of a newly described herpes virus—HHV8 (designated KSHV)—with all forms of KS (endemic, epidemic, and classical) but not with KS "look-alike" lesions, was clearly documented (60,61). Subsequent serologic evidence and prevalence statistics have bolstered this association (62,63): antibodies to HHV8 are present in almost all KS patients and commonly in HIV-l infected homosexual men but rarely in the healthy adult population. Demographic data from both cross-sectional and longitudinal studies have reinforced the thesis that HHV8 is causally related to KS and transmitted primarily through sexual contact (62,63). Whether HHV8, however, is the necessary and sufficient cause of KS remains to be proven either by fulfillment of Koch's postulates or by more stringent clinical epidemiologic evidence. Current research is addressing these epidemiologic issues and also the underlying pathophysiologic mechanisms of KS, including hormonal and cytokine-chemokine influences, and the specific molecular events (e.g. viral homology with molecular mimicry of cell cycle proteins, cytokines, and chemokines) whereby HHV8 or its gene products target quiescent lymphatic and/or blood microvascular cells to transdifferentiate or transform into rapidly

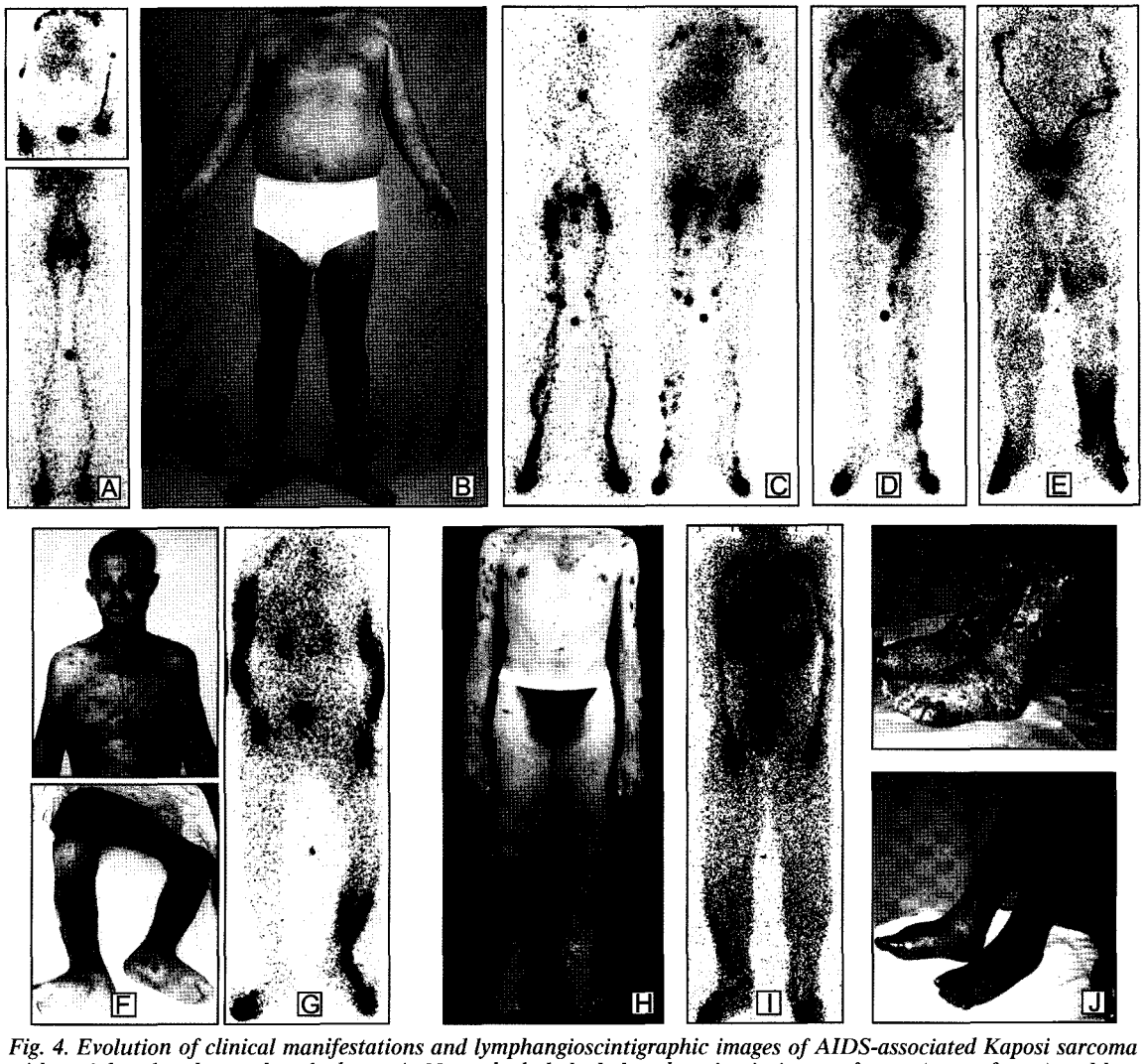

Fig. 4. Evolution of clinical manifestations and lymphangioscintigraphic images of AIDS-associated Kaposi sarcoma with peripheral and torso lymphedema. A: Normal whole body lymphangioscintigram of arms (upper frame) and legs (lower frame). Characteristic features are rapid tracer (99mTc-human serum albumin) transport without tracer dispersion (dermal backflow), and visualized regional nodes ("hot spots"). In these images, a small amount of tracer excretion into the urinary bladder is seen. Small midline "dots" represent location markers (e.g., knees, pubis, xiphoid, sternal notch). B: 43-year old homosexual male with bilateral leg lymphedema and Kaposi sarcoma-associated AIDS skin lesions. C-E show initial lymphangioscintigraphic appearance and progression of lower extremity lymphatic dysfunction (upper extremities show minimal change) over a 5-year period. C: Prompt tracer transport with focal "highlights" of tracer along calf and thigh corresponding to the sites of Kaposi lesions. During the subsequent five years (D,E), lymphatic obliteration has continued with limited tracer transport in left leg, little or no tracer migration in the right leg, and pronounced dermal backflow in both lower extremities. F: Disseminated mucocutaneous AIDS-associated Kaposi sarcoma in a 35-year old male homosexual with marked facial, torso, upper and lower extremity lymphedema. G: Whole body lymphangioscintigram showing dermal backflow without visualization of regional lymph nodes (axillary or groin) consistent with severe lymphangiodysplasia and high grade lymphatic obstruction/obliteration (compare with A). H: Advanced cutaneous AIDS-Kaposi sarcoma associated lymphedema of the legs in a 44-year old homosexual male. I: Lymphangioscintigram of patient shown in H demonstrating little or no tracer transport with pronounced distal dermal backflow (compare with A). J: Patient shown in H before (upper frame) and 6 weeks after (lower frame) extensive cleansing of skin, leg elevation with compressive bandaging-manual massage and topical antifungal and antimicrobial agents. Note the marked improvement in edema, skin texture, and overall appearance facilitating mobility.

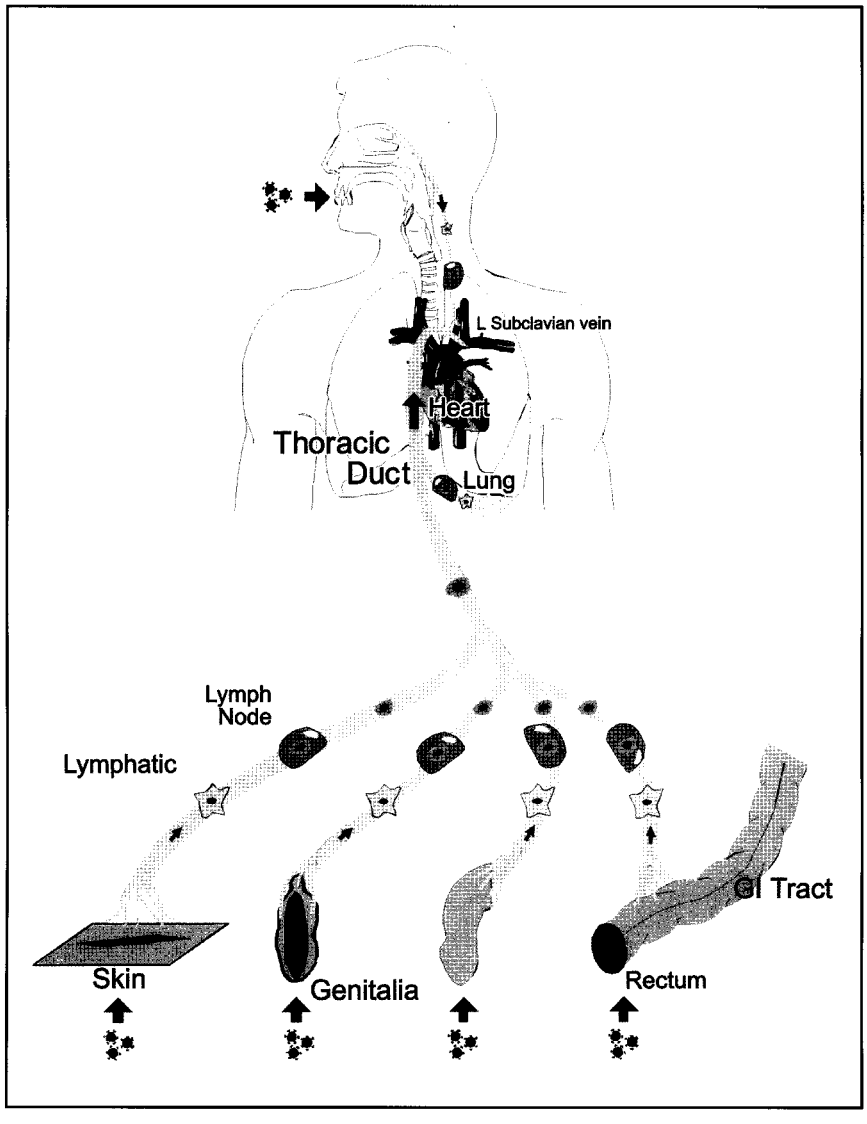

Fig. 5. Proposed primary lymphogenous route of HIV (and other microbial) infection and dissemination in infected patients where transfusions and intravenous drug abuse with direct bloodstream inoculation is absent. HIV likely enters through the mucosal barriers of the genitalia and gastrointestinal tract, including the oropharynx and skin wounds either as free particles or targeted by foreign or host mobile cells. In these forms, HIV either remains at the site of entry or migrates into draining afferent lymphatics and is transported to pelvic, mesenteric, or other regional lymph nodes gaining access to germinal centers. Infected cells and infectious particles also exit via efferent lymphatics (or alternatively via venous sinuses) and continue along lymph nodal chains into central lymph trunks and from there gain access to the bloodstream, first for pulmonary then widespread systemic dissemination. This lymphogenous route, while seldom considered in AIDS pathogenesis, bears not only on mode of entry and dissemination of HIV but also on the pathogenesis of opportunistic infections and neoplasms associated with AIDS as well as other infections.

proliferating co-mingling embryonic vascular slits and sclerotic channels *(Figs. 3 and 4)* (61-66). And why is this peculiar potentially reversible multicentric angiodysplastic/ neoplastic lesion seen almost exclusively in immunodysregulated homosexual men and so

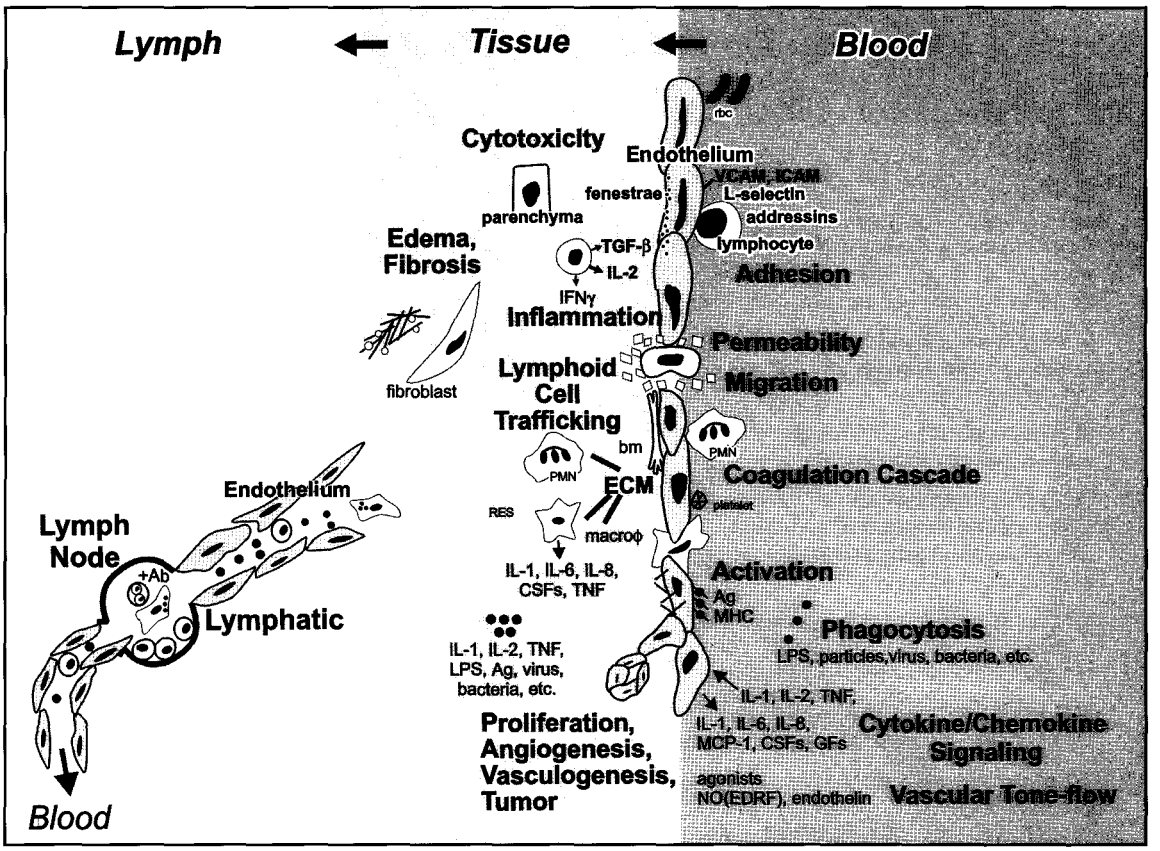

Fig. 6. Schematic illustration depicting the postulated role of the blood-lymph loop at the microcirculatory tissue level. These processes encompass micro and macromolecular permeability, vasoresponsiveness, leukocyte adhesion and transmigration, coagulation cascading, particulate phagocytosis, antigen presentation and cytokine activation, lymphoid cell trafficking, and proliferative events leading to new vessel or tumor growth. Although scarcely studied, events corresponding to those implicated at the blood vascular endothelial surface probably also occur at the lymphatic endothelial interface. Infectious particles and infected cells traverse the blood-lymph loop and trigger or are in turn swept up in these complex poorly understood interacting processes and molecular cascades. The anatomic and functional relationships between blood and lymph vascular endothelium, parenchymal and extravascular connective tissues and transmigrating leukocytes are depicted. Ab=antibody, Ag=antigen, bm=basement membrane, CSFs=colony-stimulating factors, ECM=extracellular matric, EDRF=endothelium derived relaxing factor, GFs=growth factors, ICAM=intercellular adhesion molecule, IFN=interferon, IL=interleukin, LPS=lipopolysaccharide, macro ϕ=macrophage, MCP-1=monocyte chemoattractant protein 1, MHC=major histocompatibility complex, NO(EDRF)=nitric oxide (endothelium derived relaxing factor), PMN=polymorphonuclear leukocyte, RES=reticuloendothelial system, TGF=transforming growth factor, TNF=tumor necrosis factor, VCAM=vascular cell adhesion molecule, ● = exogenous particulates, ■ = macromolecules, drops represent fluid (plasma, interstitial or lymph).

seldom in women, children, and intravenous drug abusers with AIDS?

Beginning in 1987 and subsequently biennially, the ISL sponsored AIDS-KS Ignorance Workshops and surveys have pinpointed many broadly-based questions about KS that remain to be answered definitively or even partially (53,54). Basic (Type 1) questions persist on the origin of KS spindle cells (cell type), nature of the lesion (neoplastic or multicentric hyperplastic/ dysplastic lymphatic-venous uncoupling),

TABLE 5
SAMPLE QUESTIONS ABOUT KAPOSI SARCOMA (KS)
1987-1999

TYPE 1

❑ What is *causal* (not just associated) viral agent? CMV, HIV, PPV, and now HHV8 (? other retrovirus through common pathway); same for all forms? Koch's postulates fulfilled for HHV8 necessary and sufficient?

❑ Why do only small % of HHV8 antibody positive people develop KS? Cofactor involved?

❑ What is the KS cell of origin? Cell type monoclonal or polyclonal?

❑ What is initiating event? How reversible with immune restoration? Cytokine/chemokine/viral gene product provokes KS and which combination?

❑ What is nature of lesion? Malignancy, multifocal hyperplasia/dysplasia, lymphatic/blood vascular dedifferentiation?

❑ What is relationship of angiogenesis to immunodysregulation/immunosuppression?

❑ Pathophysiologic mechanism of KS lymphedema?

TYPE 2

❑ How does KS influence course of AIDS?

❑ Does KS metastasize? How account for single localized vs. widespread lesions?

❑ Does anti-HIV, anti-HHV8 therapy ameliorate KS? Anti-angiogenesis Rx, immunotherapy, hormonal therapy work?

❑ Effects of different KS treatments on lymphedema?

❑ Why not treat KS lymphedema vigorously non-specifically with physical methods to improve quality of life?

❑ What accounts for spontaneous remission in KS?

TYPE 3

❑ Why is KS incidence high in HIV-infected male homosexuals and declining, rare in other AIDS risk group?

❑ Why so few KS cases outside risk groups?

❑ Preventive measures? Change sexual practices, eliminate which co-factors? Screen transfused blood for HHV8 antibodies?

stimulus for abnormal angiogenesis (angiodysplasia, angiotumor), and relationship to HIV infection/homosexual practices. Clinical (type 2) questions focus on how to turn the process off using angiogenesis inhibitors, chemotherapeutic agents, irradiation, antiviral drugs, cytokine/chemokine inhibitors, or shifting sex hormone balance, and how best to manage the neglected life-threatening and seriously disabling problems associated with celomic effusions and peripheral lymphedema *(Figs. 3 and 4)* (64,67,68). These latter manifestations may well reflect a lymphogenous rather than hematogenous route of infection *(Fig. 5)* that produces a fundamental disturbance in the blood-lymph loop first in the local tissues *(Fig. 6)* and subsequently at a more systemic level. *Table 5* summarizes the collected KS questions from the ISL workshops since 1987 and responses to our 1997-99 survey.

Knowledge, Ignorance, and a Research Agenda

"The reason for inventing a new theory is to drive us out of the hypothesis in which we hitherto have taken refuge into the state of thoroughly conscious ignorance which is the prelude to every real advance in science." J.C. Maxwell (69)

"Beware of false knowledge; it is more dangerous than ignorance." George Bernard Shaw (70)

"He who would be cured of ignorance must confess it." Michel de Montaigne (71)

"We answer one question and raise the next; the biggest questions will not be answered." Pierre Chambon (72)

"The Madonna of the Chair examined with a lens at a distance of 1 cm shows up quite differently than at 5 m away. The first time we see only blotches. Is then the study of blotches really the only task of the biologist?" Hans Driesch (73)

"As it stands, the existing scientific establishment, which has raised a generation of professionals to reduce scientific problems into bite-sized pieces, may not be able to effectively support the type of broad-based inquiry needed to answer the Big Important Questions (BIQs)." Roger Brent (17)

One lesson that emerges from these case studies in medical ignorance—AIDS and Kaposi sarcoma—is that the big important questions (BIQs) are the unanswered ones, and much of the explosion in basic knowledge/information is composed of precisely what Roger Brent has termed "molecular inventories." These inventories—a list of molecular aberrations and test tube correlations—have not yet been integrated into the BIQs about AIDS and KS, the questions that have persisted since the beginning of the epidemic and which surround infectious diseases in general. In large part, the immune system has not been returned to the whole body for in vivo study. The discipline of lymphology, which studies the integrated lymphatic system composed of lymphatic channels, lymph, lymphocytes, and lymph nodes has hardly been factored into the equation. We are, as Thomas lamented early in the epidemic (1) [and Rosenberg (74) recently admonished regarding events in blood (e.g., CD4 cell decline) representing a tiny (and likely deceptive) indicator of lymphoid cell trafficking (i.e., CD4 cell sequestration is occurring)] still fundamentally ignorant about the immunopathogenesis of AIDS (75). The physiology and particularly the integrated function of the "lymphomyeloid complex" (lymphatic apparatus and the reticulo-endothelial system), which includes the resident and mobile "immunocytes" such as Metchnikoff's "phagocytes," cells derived from the bone marrow, thymus, and spleen and their relationship remain poorly understood. The most fundamental aspects *(Figs. 5,6)* of viral entry, passage through vascular barriers, dissemination, and transmission as well as the battleground of the host immune response (i.e., virulence and resistance) have not yet been fully viewed in the context of the intact lymphatic circulation (the lymphogenous route) *(Fig. 5)* (53-55) and the blood-lymph loop at the tissue *(Fig. 6)* and systemic (whole body) level. It seems unlikely that a single cytokine/chemokine or even a cascade of the currently known combinations would satisfactorily explain or hold the crucial key to a chaotic feedback loop involving a constellation of interconnected cell types embedded in extracellular matrix signals that are poorly understood and inadequately researched in vivo: the task of dissecting and deciphering this big picture is still too daunting. In seriously ill patients with multisystem disorders and poorly delineated disease cofactors, the complex chaos of non-linear interdependent processes encompasses alterations in capillary permeability, vascular responsiveness, leukocyte adhesion and transmigration, coagulation, phagocytosis, and antigen presentation to cytokine/chemokine activation, lymphocyte trafficking and cell proliferation including angiogenesis and neoplasia *(Fig. 6)*. The most basic questions may not be, as one AIDS expert has stated, how to permanently lower the (HIV) viral load in AIDS and "flush out" the sanctuaries such as the lymphoid tissue or brain" (36,48,76) but rather to understand more fully the intricate biology of these inaccessible sanctuaries that both protect and endanger the host when HIV and other coinfecting microorganisms gain entry. As pioneer lymphologists Yoffey and Courtice (77) summarized nearly three decades ago, "From experimental evidence on filtration by

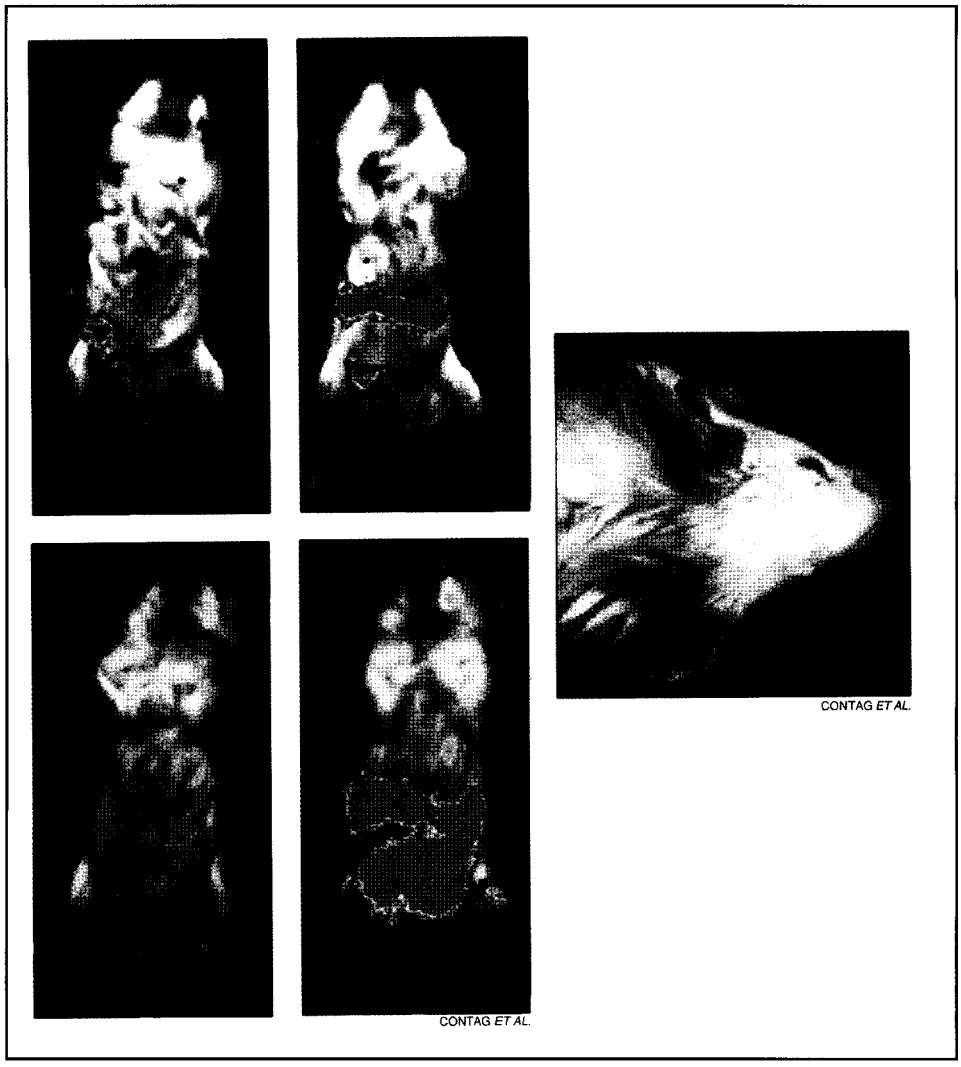

Fig. 7. Red glow (seen here as homogenous grey enclosed area) that appears on a videocamera image when luciferase (enzyme for firelight in fireflies) gene is turned on in a luciferase transgenic mouse by infection with luciferase gene spliced salmonella bacteria. (right) Taken 5 hours apart, the course of infection when untreated (left pair) and when treated with antibiotics (center pair) is shown. In the mouse, the luciferase gene is tied to a genetic switch that, in human cells, is activated when HIV is replicating. [Reproduced with permission from C. Contag (80)]. Such in vivo imaging illustrates the dynamic pathophysiology of infections in real time, providing a powerful clue to the underlying biomechanisms, as well as direct visual quantifiable evidence of effectiveness of a variety of therapeutic approaches from antimicrobials to gene transfer.

lymph nodes, inanimate particles (arriving in afferent lymph) are held up ... to a considerable extent ... depending on the degree of saturation of the phagocytic capacity of the reticuloendothelial cells. Bacteria are fairly efficiently filtered out ... Vaccinia virus is filtered out very inefficiently ... In fact, as far as viruses are concerned, lymph nodes may be a source of danger rather than of safety, since they may actually serve as centers for the initial propagation and subsequent dissemination of virus

throughout the body..." As far back as 1939 (78), Yoffey had documented the early and rapid entry within hours of intranasally instilled vaccinia virus into lymphatic channels and regional lymph nodes experimentally; he extended this insight to HIV infection and AIDS in 1989 (79). Such classical teachings stress that after introduction of virus through skin and mucous membranes, lymphoid tissue is the primary anatomic site for processing, spreading, replication, initial establishment and subsequent reservoir/formation of a viral infection. Yet, only in the last several years has this "truism" been rediscovered. Clearly, the lymphoid reservoirs need to be made more accessible to study and manipulation, e.g., by minimal or non-invasive imaging *(Figs. 3-4)* (63) and sampling (80-82). How much more there is to learn as we move from static snapshots of the sites of HIV residence/replication and immune response (83) to dynamic in vivo images and direct sampling of central or regional lymph (as we discovered several decades ago by thoracic duct and regional lymphatic cannulation) entering and exiting the sanctuaries in animal models of AIDS and in patients. Access is now possible less invasively through specially adapted vascular endoscopes, which would allow direct testing and quantification of the lymphogenous as well as hematogenous route of infectious spread. Imagine the panorama of in vivo images using bioluminescence (84) *(Fig. 7)* or radioactive or magnetic tracers *(Figs. 3,4)* to produce "molecular angiograms" to track these events and the influence of therapeutic agents including gene transfers and to uncover what lies hidden in the fluids bathing and circulating through these infected, immunologically reactive sites. The third and most neglected therapeutic approach for AIDS (after antivirals and vaccines) and KS is a panoply of immunorestorative agents and approaches [viz. in (7) Thomas and (51) Lederberg], which rests on this understanding as do also the other two modalities ["flushing" out HIV from the lymphoid reservoirs (antiretrovirals) and vaccine development], i.e., the lymphogenous route of viral entry and spread and the source of immune response.

Our own personal forays as lymphologists (indeed, "lymphomaniacs") exploring a potpourri of other infectious processes [tuberculous enteritis (85), post-operative infections (86), overwhelming post-splenectomy sepsis (OPSS) (87-90), lymphatic filariasis (91,92), opportunistic infections associated with peripheral and visceral lymphedema syndromes (93,94) and Whipple disease (95,96)—their pathogenesis, evaluation, management, and social context] lead us to believe that the history and lessons of the AIDS/KS ignorance scenario apply just as well to these other infectious conditions (see Addendum for Ignorance Rounds on Tularemia). The fundamental unknowns crucial to eventual understanding and improved treatment and prevention revolve around how the particular "germ" (virulence, life cycle, and compatibility) and the host (and larger societal) "terrain" (protective and promoting) interact within the blood-tissue-lymph loop to produce the particular manifestations, spectrum, tempo, and responsiveness of the disease in an individual patient. And similar unanswered BIQs surround these problems, too: Is Crohn's regional enteritis due to a similar as yet unidentified fastidious bacterium like the tubercle bacillus or a virus that produces chronic lymphatic obstruction with lymphedema culminating in the "garden hose" texture of the small bowel? In OPSS precipitated by pneumococci and other encapsulated microorganisms, what exactly does the spleen do (that the liver and lymph nodes can't) to contain this spectrum of pathogens? Is a little bit of spleen (splenic preservation), and how much, better than none at all? How can splenic protective immunity be restored in an asplenic host: are there effective "splenomimetic" agents and improved operative approaches to splenic preservation? In lymphatic filariasis, how do

the adult filarial nematodes come to live and mate in what filariologist Kumaraswamy has termed the immunologic "police station" of the body? Do the adult worms feed on the lymphocytes/phagocytes sent to attack them? Are the microfilaria more damaging (obliterating lymphatics by inflammatory response) dead than fertile and alive (producing lymphangioparalysis)? Can they be eradicated by genetic/molecular biologic approaches or will prevention (public health measures, e.g., sanitation and vector control, absent vaccines) prove to be the only effective approach? In "opportunistic" infections that develop in the setting of peripheral and visceral lymphedema, what properties of the altered lymphedematous tissue terrain make these patients so susceptible to a wide variety of organisms of low pathogenicity and even "opportunistic neoplasms" (such as angiosarcoma closely resembling aggressive KS). It is as though these patients suffer from a form of "local AIDS" confined to the swollen limb (or inadequate drained organ system) with a localized disruption of the "blood-lymph loop") (55,93,94).

During preparation of this article, many of the "distinguished AIDS ignorami" whom we surveyed surmised that a multitude of other disorders of unknown (or incorrectly presumed known) etiology will eventually turn out to be infections. Several also suggested that anti-retroviral therapy including protease inhibitors (or other antibiotics) may have non-HIV specific salutary (and adverse) effects on coinfecting microorganisms not to mention host cells in AIDS. After all, it is only in the past decade that Helicobacter pylori has proved to be the etiologic agent of most peptic ulcers (and perhaps also gastric lymphoma and carcinoma), opening the way to a cure of ulcer disease in most patients by specific antibiotic treatment. Similarly, with Whipple disease, peliosis hepatis and bacillary angiomatosis (97), infectious disorders that occasionally complicate AIDS, the long suspected but elusive pathogens have now been identified and efficacious antimicrobial regimens instituted often with cure. Most intriguing is the recently proposed association of Chlamydia pneumoniae (and also CMV) with atherosclerotic plaque, raising the distinct possibility that a variety of vascular lesions not considered to be of infectious etiology (98), including some found in patients with AIDS, are associated or even caused by the newly catalogued agent of cat scratch disease or other common bacteria or viruses. Indeed, how many chronic idiopathic or "autoimmune" disorders and other poorly understood pathologic processes [e.g., even kidney stones formed from calcium shells of tiny nanobacteria (99)], particularly those of a slowly progressive unremitting nature, are due to yet to be discovered (or old familiar) infectious agents? And how many infectious disorders do we bring on ourselves from food contamination, environmental pollutants and a greatly expanded pharmacopoeia? As the world (and universe) becomes smaller and more interconnected (100), what other microorganisms emerging and reemerging, new, unrecognized, and often resistant that are lying in wait in hospital corridors, tropical climes, biologic weaponry, and in samples of outer space (101)? How, on the other hand, can microbes be used as bioreactors and their wiles curbed to attack disease processes such as cancer and genetic defects?

As pointed out earlier, Type 3 (societal) questions are just as vexing ranging from economic disparities in access to care, legal ramifications of discrimination and mandatory testing/treatment, and sexual taboos, to the burgeoning profit motive (greed, glory, insider trading), conflicts of interest, and fraud in drug development, biotechnology, clinical trials, and the doctor-patient relationship. How best and by whom should priorities be set in the medical research-action agenda and what are the best approaches to bridge the link between basic biology and the patient? How should funds be allocated to assure that physician-scientists and other researchers capable of carrying out broad-based translational clinical research in the

public interest do not become an extinct species especially in the managed care environment where fiscal constraints misdirect medical schools and teaching hospitals away from their academic mission toward corporate welfare supported by the taxpayers? And what should the public be told and not told and how much optimism (hope vs. hype) and pessimism (gloom, doom) (viz. 46-49), "realism" (102) should the scientific community convey in its messages to each other (hypotheses and null hypotheses) and to the public? What checks and balances should be in place so that the average citizen becomes sufficiently scientifically literate and supportive of research yet realistic about the ramifications of science's collective ignorance and the tentative, tenuous nature of inquiry and knowledge? How much truth can (and should) the public be told? What is the healthy dose of "ignorance" which when mixed with information updates serves to advance science, educate physicians, promote sound medical practice, and inform and involve the public?

EPILOGUE

"Public policy must attack... the social stigmas associated with sexually transmitted diseases and drug abuse as well as the germs that cause it (the contamination aspect - the breeding grounds or channels of spread) if we expect to apply the "true remedies" that will successfully control [their] spread." Yankauer (103)

"Germs, germs everywhere... 'hot zones' of bacteria in your kitchen and bath areas. The more tidy the household the more widespread the bacteria." Parade Magazine (104)

"Pathogens are usually one step ahead of the host." Heidi Pleogh (105)

Based on mathematical modeling of geometric (ordered connections) contrasted with ring lattices (random connections), *"infectious diseases are predicted to spread much more easily and quickly in a 'small world' and it is alarming how few short cuts are needed to make the world small."* Samuel Strogatz (106,107)

"It is the mountain of the unknown that spurs scientific progress...our progress is impeded by true ignorance: lack of familiarity with that which is known and lack of comprehension of the need for–and the very nature of–the process of biomedical research." Nobel Laureate Thomas Weller (19)

"We are all taught what is known, but we rarely learn about what is not known and we almost never learn about the unknowable. That bias can lead to misconceptions about the world around us." Alfred P. Sloan Foundation President Ralph Gomory (108)

"Through seas of knowledge we our course advance, / Discov'ring still new worlds of ignorance; / And these discov'ries make us all confess / That sublunary science is but guess." William Derham (19)

"In the sense of unaware and as yet unlearned our ignorance and our recognition of that ignorance may be the best motivation both for problem solving and for creative activity." Norman Hackerman (109)

"Thus, science for Homo economicus [devoted to profit] and homo faber [devoted to immediate use to industry] is flourishing while science for Home sapiens is diminishing... the ascent of man has [therefore] been left in the care of Homo ignorantis... and new science." Takashi Tachibana (110)

"Man needs not only knowledge but ignorance, too. Knowledge alone, or ignorance alone, leads him into darkness...The world is so filled with the matter of knowledge that men would go mad if they were to attempt to cram all of it into their heads. The ability to forget is just as necessary as the ability to remember." Vinoba Bhave (19)

Since we began this article with reflections of visionary physician Lewis Thomas on the emerging AIDS epidemic, Thomas also should have the last word on blending of Homo sapiens with Homo ignorantis:

"The thing to do, to get us through the years just ahead [the next millennium], is to

celebrate our ignorance. Instead of presenting the body of human knowledge as a mountainous structure of coherent information capable of explaining everything about everything if we could only master all the details, we should be acknowledging that it is , in real life, still a very modest mound of puzzlements that do not fit together at all... we have such a distance still to go." (111)

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1997-1999 survey *(Tables 4 and 5)*: F. Barre-Sinoussi, M. Dictor, D. Francis (Vaxgen, California), H. Gendelman (University of Nebraska, Omaha), A. Gottlieb,* J. Levy (UCSF, CA), J. Marchalonis, R. Root-Bernstein, H. Shapiro (H. Shapiro, PC, West Newton, MA), G. Weissman (New York University School of Medicine, New York City), C. Witte (University of Arizona, Tucson) and M. Witte
*deceased

ADDENDUM

In March, 2000, the authors presented "Considering Tough Infectious Diseases Problems From the Perspective of Medical Ignorance" at the University of Utah Center for Infectious Diseases, Diagnostic Microbiology and Immunology. This Medical Ignorance Rounds was organized by Professor of Medicine Zell McGee, an expert in the mechanisms and clinical aspects of sexually transmissible (particularly gonococcal) diseases, who had previously served at The University of Arizona College of Medicine as a visiting "distinguished ignoramus" in 1991 and is a long-time disciple of Lewis Thomas since his days as a Bellevue Hospital house officer. The Rounds centered on a patient unknown with an acute history of high fever and tender right cervical lymphadenopathy tentatively diagnosed as Hodgkin disease. Following a standard consideration of the appropriate workup for diagnosis, the ignorance aspects were considered not only in terms of unanswered questions (basic, clinical, and societal) about the patient's ailment but also about medical

history (Galen and Pasteur), cognitive dissonance, and the nature of science. Others probed the relationship of host response to the possible infectious agent, the nature of lymphadenopathy in this circumstance, predilection for the lymphogenous route, regional nature of the condition suggesting possible entry point into the lymphatic system at the undisclosed eschar from the bite of a yellow-bellied deerfly. The likely diagnosis of tularemia was pinpointed, a definitive serologic diagnosis (causative agent now identified as Francisella tularensis) made, and an appropriate antibiotic regimen instituted, with prompt defervescence and regression of cervical lymphadenopathy. A similar case of "tularemia and the tomcat" (112) was cited. Lingering questions were then further considered where ignorance abounds in the germ vs. terrain debate so eloquently captured by Pasteur.

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