Biomedical Science

Medical Ignorance, AIDS-Kaposi's Sarcoma Complex, and the Lymphatic System

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In the introduction to the *Cecil Textbook of Medicine*, Lewis Thomas, whose prize-winning collections of essays on biology have delighted both the medical profession and the lay public, gives a unique prescription for what ails medical education. Since, he reasons, the greatest single achievement of science in this most scientifically productive of centuries is the recognition that we know very little about nature and understand even less, he wishes there were "some formal courses in medical school on Medical Ignorance; textbooks as well, although they would have to be very heavy volumes. We have a long way to go."[1(pxliii)] Ironically, celebrated medical triumphs flowing from the information and technology explosion often do reveal most notably our ignorance: that which we don't—but need to—understand. The Curriculum on Medical Ignorance (Figure 1, top), begun in 1985 at the University of Arizona College of Medicine, aims to help students recognize and deal with this vast intimidating world of nonknowledge composed of the things we know we don't know, the things we don't know we don't know, and the things we think we know but don't.[2-4] Our goals (Table 1) are to enlarge the understanding of the shifting domains of medical knowledge, uncertainty, ambiguity, and the unknown and how one decade's facts become the next's follies and vice versa; improve skills in working within this context; and develop the needed attitudes to recognize and deal with ignorance. Activities (Table 1) include a summer institute of full-time hands-on basic and clinical research and workshops largely for first- and second-year students; a clinical elective, "Seminars and Clinics on Medical Ignorance," for third- and fourth-year medical students; and a seminar series featuring visiting professors of ignorance, that is, "distinguished ignoramuses" who are not only leading experts in their discipline but also have keen insight into the great unknowns and are willing to admit their limitations.

The central thrust of these experiences is the reverse of most medical curricula—that is, learning how to question, rather than how to answer, whether about the basic biology of an illness (type 1 ignorance questions); the diagnosis, prognosis, and treatment of specific diseases (type 2 ignorance questions); or related socioeconomic, legal, and ethical issues (type 3 ignorance questions). The House of Ignorance (Figure 1, bottom)—*La Residencia del Incognitó*—across the street from the University of Arizona Cancer Center provides a congenial book-free atmosphere for unknowers, including students, mentors, and visiting professors, who gather together and explore the cutting edge of the unknown. Students are graded not by short-answer tests, but primarily by the progression of their questions, which they record serially in weekly "ignorance logs" as they explore, analyze, discuss, carry out research, and practice making clinical decisions where lives may hang in the balance. Student evaluations praise this curriculum for "bringing home how ignorance abounds," "offering time and encouragement to put things into perspective," "reinforcing a thirst for knowledge," "awakening curiosity and enthusiasm dampened by excessive passive learning," and "demonstrating that it takes a lot of effort and knowledge to appreciate ignorance and find the most important questions that aren't, rather than are, answered in a field." Thus, some of our best students, by dint of hard work, probing intellect, and resourcefulness, are leaving the University of

TABLE 1.—*Goals and Methods of the Curriculum on Medical Ignorance at the University of Arizona College of Medicine*

Curriculum Goals	*Activities and Courses*
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	Summer Institute on Medical Ignorance Seminars and Clinics on Medical Ignorance Full-time basic and clinical research Questions and questioning exercises Creative thinking exercises Final oral and written reports on se'ected topics in Medical Ignorance Weekly ignorance logs Visiting professors of Medical Ignorance La Residencia del Incognitó
Improve skills to recognize and deal productively with ignorance, uncertainty, and the unknown: question critically and creatively focus on raising, listening to, analyzing, prioritizing, and answering questions from different points of view; communicate clearly in different media with various audiences; collaborate effectively with different people and other resources	
Reinforce positive attitudes and values of curiosity, optimism, humility, self-confidence, and skepticism	

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

Arizona College of Medicine more ignorant than when they entered!

In this discourse, we will present, with the aid of only one Western blot, a personal odyssey in medical ignorance stretching over the past several decades from the ghettoes of St Louis to the golden temples of India, exploring swollen limbs and swollen bodies through the eyes of lymphologist-lymphomaniacs, coursing back and forth from blood to lymph to gain a glimmer of understanding about an odd group of disfiguring, disabling, and, at times, life-threatening disturbances of the lymphatic system (Figure 2). An array of fragmentary ideas, false starts, and some chance discoveries also happened along the way.

Our story begins more than 20 years ago in September 1968 in the now-defunct St Louis (Missouri) City Hospital, where we first encountered a teenager with brawny swollen legs and elephantine genitalia of several months' duration (Figure 3),[5] which he traced back to several heterosexual encounters. He had not traveled outside the St Louis area, nor had he received blood transfusions or abused drugs. Dorsal pedal lymphangiography displayed complete lymphatic obstruction at both groins with dermal backflow of the oil contrast medium; an excised inguinal lymph node showed marked fibrosis. Over the ensuing 15 months, his clinical course was progressively downhill with intermittent fever, ascending body wall lymphedema, recurrent bilateral pleural effusions, and a 23-kg (50-lb) weight loss. Chlamydial microorganisms were repeatedly identified in blood and body fluids, and hypoproteinemia and pronounced peripheral lymphocytopenia progressively worsened despite aggressive antimicrobial therapy. At autopsy, not only was a solitary purplish cutaneous nodule of Kaposi's sarcoma visible on the medial aspect of his right thigh, but much of the edematous fibrotic soft tissue throughout the body, including the chronically inflamed anorectum,

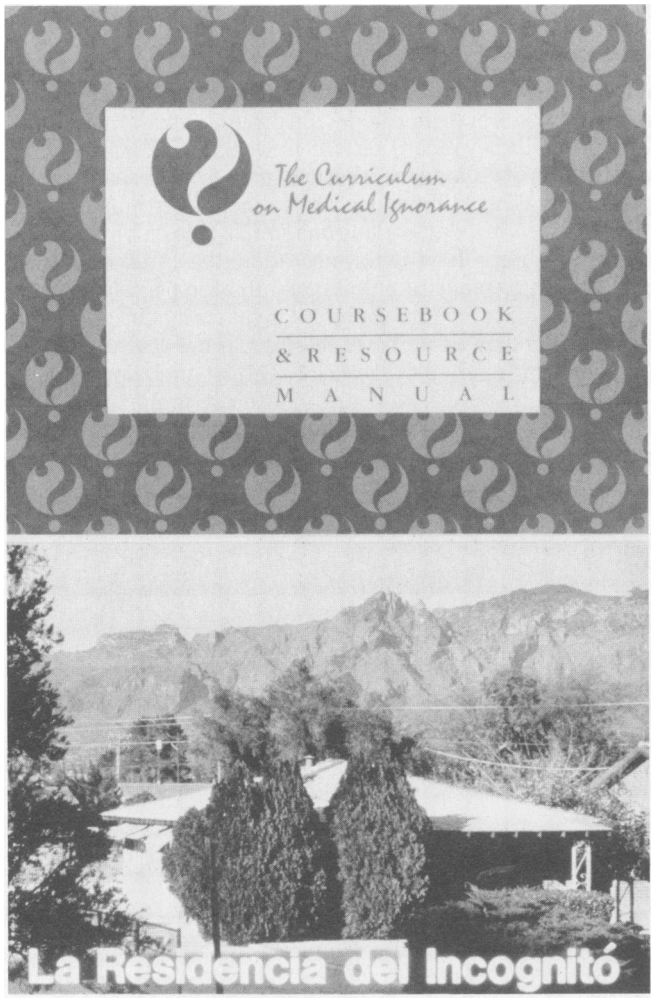

Figure 1.—The top photo is of an instructor's guide for teaching the Curriculum on Medical Ignorance, and the bottom photo shows the House of Ignorance *(La Residencia del Incognitó)*, dedicated to students and faculty exploring medical unknowns together.

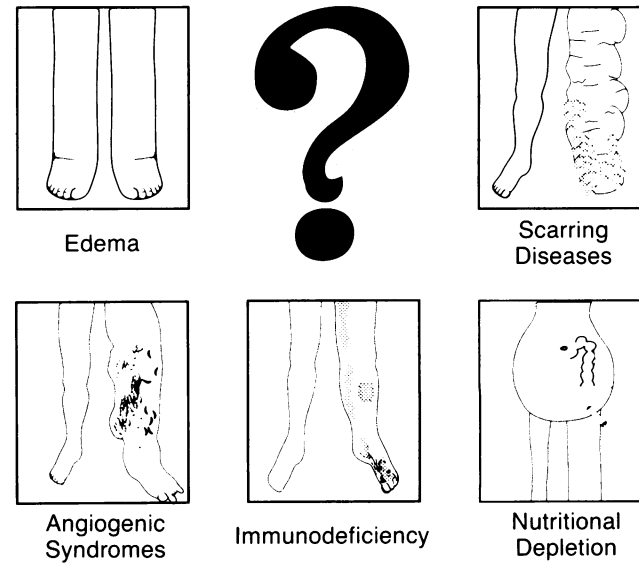

Figure 2.—There is a puzzling constellation of findings in disorders of the lymphatic system.

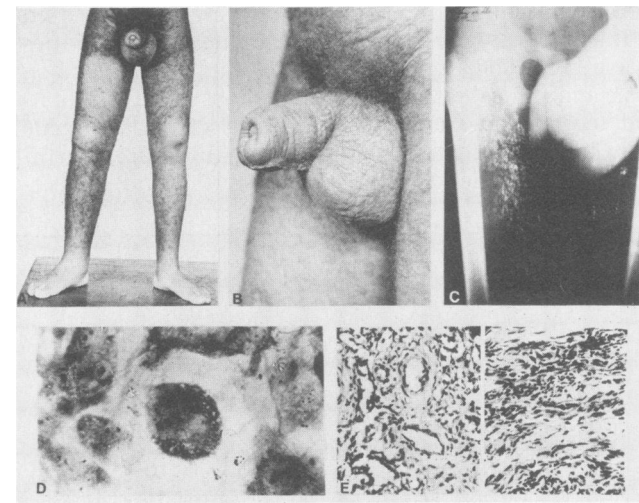

Figure 3.—The photos illustrate case study in medical ignorance #1: The initial appearance **(A,B)** of a 15-year-old adolescent boy with pronounced swelling of the penis, scrotum, and lower extremities. Genitalia show brawny edema and minute cystic swellings representing lymphatic vesicles on the penis and scrotum. Conventional lymphography **(C)** reveals obstruction of leg lymphatics at the groin with dermal backflow. A photomicrograph **(D)** of irradiated McCoy tissue culture of ascitic fluid obtained at postmortem shows "initial bodies" (dark cytoplasmic blebs), an intracellular phase of *Chlamydia* species (original magnification × 750). Photomicrographs **(E)** of groin subcutaneous tissue show abnormal lymphatics lined by atypical endothelial cells with pleomorphism and hyperchromatic nuclei (hematoxylin and eosin, × 416). Questions abound (see text). (From Elvin-Lewis et al,[5] reprinted with permission.)

was infiltrated with a vascular malignant lesion variously interpreted as Kaposi's sarcoma or lymphangiosarcoma. Lymph nodes, spleen, bone marrow, and thymus exhibited profound lymphocytic depletion with few precursors, extensive fibrosis, and scattered Kaposi's lesions.

At that time, we were at a loss to put a name on this patient's ailment, nor could we find previous reports of a similar constellation of findings—swelling, scarring, wasting, immunodeficiency, and uncontrolled angiogenesis. As busy clinicians and investigators, this was not our first brush with medical ignorance, nor would it be our last, but it was the one that was to stick most vividly over the years in the comfortable but almost forgotten "attic" of our collective brains. This "attic of the brain" Thomas views as the

> darkest and strangest part of the building, reachable only by placing a stepladder beneath the trapdoor and filled with unidentifiable articles too important to be thrown out with the trash but no longer suitable to have at hand.... all the things deposited in it became, one by one, lost to consciousness. But they were still there . . . safely and comfortably stored in the tissues of the house . . . [a] place for functionless, untidy, inexplicable notions, [the] dark comfortable parts of the mind to hide away the things we'd like to keep but at the same time forget.[6(pp138,140)]

In 1973 when we published a detailed report of this case in the journal *Lymphology,*[5] the group of physicians who had cared for the patient had gone their separate ways, our team to the new University of Arizona College of Medicine. We continued investigations, delving into the mysteries of body swellings from high-output failure of the lymph circulation where an overworked lymphatic system, despite accelerated flow, still fails to drain fully excess tissue fluid arising from an imbalance in the Starling hydrostatic and oncotic forces at the capillary-tissue interface.[7,8] For example, patients with portal hypertension from hepatic cirrhosis, whether or not ascites is present, uniformly show staggering increases (sixfold or more) in central thoracic duct lymph flow. How do some cirrhotic patients turn into frogs with lymph hearts pumping back many times their plasma volume daily but still not enough in some to keep pace with lymph formation, so that ascitic fluid accumulates with disastrous consequences? Yet treatment aimed at reducing excessive splanchnic lymph formation by portal decompression through a portasystemic shunt, or at accelerating lymph absorption through a megalymphatic peritoneovenous LeVeen shunt, may restore the balance between the formation and absorption of lymph, and ascites recedes. But all swellings are not alike. In contrast to the pitting, water-logged tissues of the high-flowing lymph states from venous hypertension, the high-protein brawny edemas from low-output failure of the lymph circulation, as in lymphatic blockade, provoke progressive tissue fibrosis, intense neovascularization, and fat deposition, as exemplified by elephantine limbs with their striking resemblance to a cirrhotic liver and the leonine facies of lepromatous leprosy.[7,8] And why is lymphedema so hard to undo? We begin to envision a more encompassing blood-lymph circulatory loop transporting, or, in disease, failing to transport, not only liquid and small solutes but also macromolecules, particles, and lymphoid cells through tissues, lymphatics, and lymph nodes back to the bloodstream and around again and again.

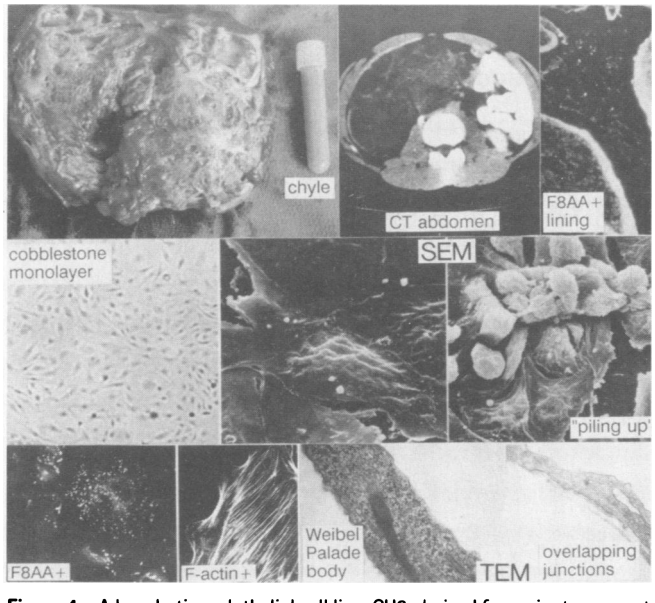

Figure 4.—A lymphatic endothelial cell line, CH3, derived from giant recurrent retroperitoneal lymphangioma raises questions about the link between lymphatic malformations and neoplasia. The top row shows, **left to right,** an operative specimen with chylous contents, a radiolucent mass on abdominal computed tomography (CT), and cyst lining immunofluorescence for endothelial marker, factor VIII-associated (F8AA+) antigen. CH3 displays cobblestone morphologic features **(middle row, left)** and on scanning electron microscopy (SEM; **middle** [original magnification × 471] **and right** [× 114]) is composed of polygonal cells, in some areas "piling up," that are positive for factor VIII-associated antigen and F-actin **(bottom row, 2 left photos** [× 80 and × 266, respectively]**).** On transmission electron microscopy (TEM), the polygonal cells contain Weibel-Palade bodies and show lymphatic-like overlapping intercellular junctions **(2 right photos** [× 6300 and × 1900, respectively]**)** (from Way et al,[13] reprinted and made into composite with permission).

Time passes rapidly, and it is already 1981. Simultaneously on the East and West coasts, a perplexing new clinical syndrome[9,10] is attacking young gay men, causing profound immunodeficiency, rare opportunistic infections, and that same unusual skin cancer of our patient, namely, Kaposi's sarcoma. The striking resemblance of this new acquired immunodeficiency syndrome to that of our St Louis patient from 1968 prompts us (M.H.W., C.L.W.) to write a letter in 1984 to the *Journal of the American Medical Association.*[11]

New questions arising in the clinic and laboratory concerning a constellation of overlapping findings in lymphologic syndromes once again distract our attention from the strange case described here. Intrigued by the isolation of long-lived lymphatic endothelial cell lines from lymphatic malformations and tumors such as a massive, rapidly growing, cervicomediastinal cystic hygroma associated with diffuse bony lymphangiomatosis[12] and a giant, recurrent, cavernous, chyle-filled retroperitoneal lymphangioma (Figure 4),[13] we begin to question the fine line between congenital anomalies and true vascular neoplasia and between benign and malignant growth. A proliferation of both lymphatics and blood vessels, that is, lymphangiogenesis and hemangiogenesis, and even the formation of vascular tumors (angiotumorigenesis) seem to play a central role in syndromes of lymph stasis (Figure 5).[14,15] This angiogenic process is often preceded or accompanied by fibrosis, lipid deposition, recurrent opportunistic infections, and impaired immunity, which is limited to the lymphedematous areas and related in part to locally defective clearance and antigen-processing mechanisms. Furthermore, reduced circulating T-helper lymphocytes in conjunction with lymph nodal and thymic atrophy, diffuse fibrosis, vascular transformation, and malignant lymphomas are prominent features of various lymphedema and chylous syndromes. Rarely, as after radical mastectomy, a chronically lymphedematous extremity is the site of a highly aggressive malignant vascular neoplasm, the so-called Stewart-Treves syndrome.[16] Indeed, we initially labeled our patient's vascular tumor an "angiosarcoma," and he represents the purest personification of this entire conceptual scheme, showing not only "local acquired

immunodeficiency syndrome (AIDS)" from uncontrolled lymph stasis in a single limb but also the systemic manifestations in macrocosm.

By now the human immunodeficiency virus (HIV) has been isolated from patients with AIDS, and specific serum tests have become available. To our surprise, we identify circulating antibodies to nine of nine HIV type 1 antigens as well as specific retroviral protein in specimens of our patient's body fluids and tissues frozen in ignorance for nearly 20 years (Figure 6).[17]

Although we had forged a curious biologic link to the past, its meaning was unclear and troubling. Had AIDS actually been around a long time, perhaps even millennia, and maybe did not arise in Africa but emerged as an epidemic and ultimately a pandemic because of some bizarre

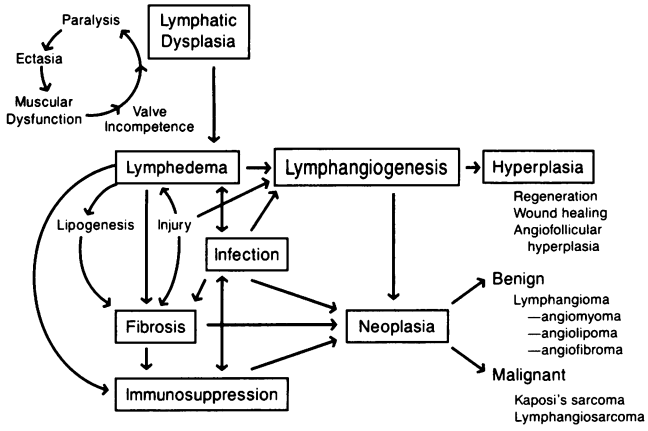

Figure 5.—The diagram illustrates some poorly understood links between lymphangiogenesis and disorders of the lymphatic system characterized by lymph stasis. See text for details (from Witte and Witte,[14] reprinted with permission).

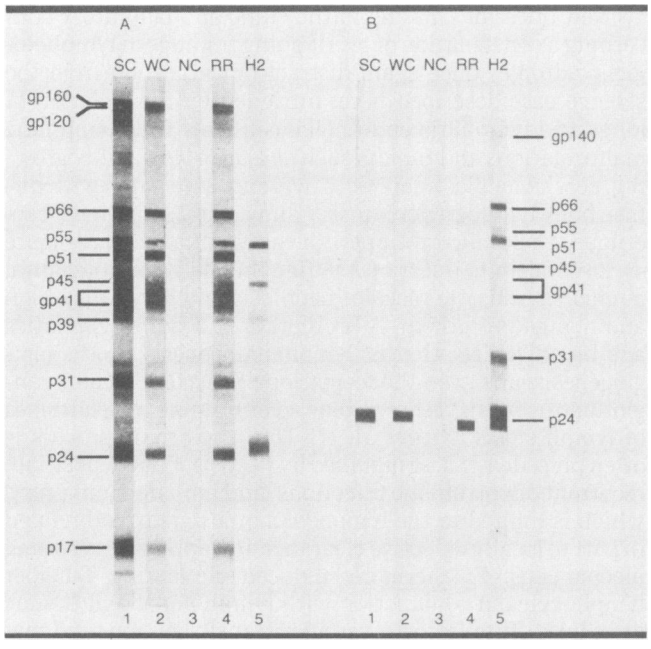

Figure 6.—Western blot reactivity against human immunodeficiency virus (HIV) proteins occurs in serum from a 15-year-old boy initially seen in 1968: panel A shows reactivity against HIV-1 protein, panel B shows reactivity against HIV-2 proteins. Lane 1 (SC) indicates strongly reactive HIV-1-positive serum; lane 2 (WC) has weakly reactive HIV-1-positive serum, lane 3 (NC) shows nonreactive control serum, lane 4 (RR) indicates patient's serum (April 16, 1969), and lane 5 (H2) indicates HIV-2-positive serum. This observation raises more questions than it answers (from Garry et al,[17] reprinted with permission [copyright 1988, American Medical Association]).

environmental coincidence? And, would our patient have been better off today with all that we have come to know about this dread syndrome? Unfortunately, no. His disease probably would have been just as rapidly fatal now as in our primitive bewilderment back then, highlighting once again how much ignorance surrounds the explosive core of medical information and biotechnology.

Whereas a Chicago *Tribune* headline hails these findings as "shaking theories of AIDS origin" (J. Crewdson, Chicago *Tribune*, October 25, 1987, p1), this patient's case also exemplifies the interconnectedness of the lymphatic system's four components—lymph, lymphatic vessels, lymph nodes, and lymphocytes—and how closely linked the unhinging of the blood-lymph loop of fluid, macromolecules, and migrating cells is to the processes of swelling, scarring, wasting, immunodeficiency, and angiogenesis.

How, then, can these concepts help to delineate the approach to treatment of these lymphologic syndromes (Figure 7)? First, edema arises when the circulation of tissue fluid or lymph fails, whether in cases of high- or low-output imbalance. When macromolecular movement is also impaired, as in long-standing high-protein lymphedemas, scarring disorders appear. As the migration of lymphoid and other mobile cell populations—particularly the antigen-presenting complex—through tissues, lymphatics, and interposed lymph nodes becomes restricted or disordered, or, alternatively, when lymph is either sequestered internally or lost directly to the outside, immunodeficiency and nutritional depletion syndromes develop. Exuberant angiogenesis and even angiotumorigenesis of lymphatics, blood vessels, or both often accompany or may precede these other abnormalities, presenting as benign or malignant vascular tumors. Lymphatic disturbances of widely different etiologies—genetic, congenital, and acquired—may be localized to a single limb or internal organ, or may involve the whole body (Figure 8).[18] Animal counterparts are also found in nature or can be induced experimentally. When a disorder of the blood-lymph loop is suspected, a comprehensive rational workup can be carried out at the bedside, in the imaging suite, operating room, and laboratory (Figure 9).[19] Using time-honored tools updated to the modern era of molecular biology, lymphologists visualize, sample, analyze, and thereby characterize the disorder. In vivo, lymphatics and nodes are imaged directly by vital dye injection and oil-contrast lymphography or noninvasively by magnetic resonance imaging, fluorescent videomicroscopy, in-

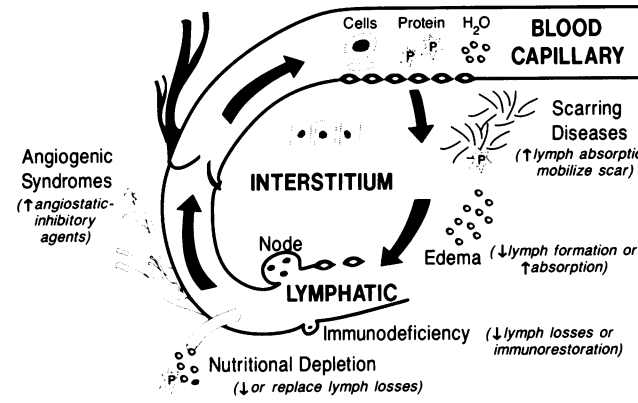

Figure 7.—Characterized, in the face of ignorance, are clinical disorders of the blood-lymph circulatory loop of fluid, small solutes, macromolecules, and cells manifesting as swelling, scarring, immunodeficiency, nutritional depletion, and uncontrolled angiogenesis and angiotumorigenesis. The phrases in italics in parentheses designate therapeutic approaches. See text for details.

direct lymphography, and, most important, by lymphangioscintigraphy after the simple intradermal administration of radioactive protein.[19] Central or regional lymphatics can be cannulated to determine tissue fluid fluxes and lymph and edema fluids analyzed for chemical and cellular constituents. Thus, the anatomic, biochemical, and physiologic disturbance of the blood-lymph loop, whether from lymphatic overload, lymphatic obstruction, or external lymph loss, can be delineated in vivo. In addition, components of the blood-lymph loop can be removed from the body, including lymphatic segments, endothelium, or lymphocytic subpopulations. The tissue or lymphatic microenvironment can then be recreated in vitro, for example, to assess lymphatic contractility or the movement of proteins and lymphocytes across endothelial monolayers or to determine why the "criminal" adult filarial worm (Figure 10), surrounded as in life by human lymphatic endothelium, lymph, and lymphocytes, chooses to dwell in what Indian filariasis researcher Kumaraswamy has called the "police station" of the body, and the "cops do nothing about it."[20]

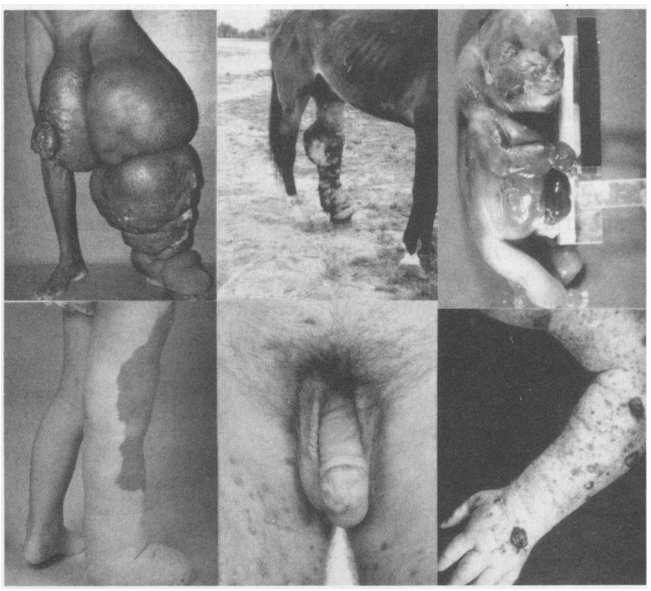

Figure 8.—These are dramatic examples of the wide variety of genetic, congenital, and acquired disorders in the curious spectrum of lymphologic syndromes: **Top,** left to right, lymphatic filariasis (courtesy S. Jamal), posttraumatic lymphedema, fetal Turner's (XO) syndrome with strangulating cervical cystic hygroma and hydrops. **Bottom, left to right,** Klippel-Trenaunay syndrome, acquired immunodeficiency syndrome-associated Kaposi's sarcoma, and Stewart-Treves lymphangiosarcoma from postmastectomy lymphedema (the last from Stewart et al,[16] reprinted with permission).

Finally, when the disorder of the blood-lymph circulatory loop is pinpointed and characterized in vivo and in vitro, rational therapeutic approaches (Figure 7, italics in parentheses) can be devised and then evaluated by their efficacy in normalizing the blood-lymph loop. For example, in swelling and scarring syndromes, efforts are directed at reducing lymph formation or enhancing lymph absorption and mobilizing scar tissue. Depleted nutritional elements are repleted by halting bulk lymph losses. The deficient cellular or humoral immune system is reconstituted by redirecting migrant lymphoid streams or selectively replacing specific cellular subpopulations. Angiogenic syndromes can be retarded using angiostatic and angioinhibitory drugs. Unfortunately, these rational therapeutic goals are still more often than not unattainable in our present state of ignorance.

The following two kaleidoscopic examples illustrate how the previously hidden lymphatic circulation is finally coming into clinical view to be probed down to the cellular and molecular level and ultimately manipulated. First (Figure 11), in a gay man with AIDS-associated Kaposi's sarcoma, a lesion long thought to derive from lymphatics and to block them,[21,22] lymphangioscintigraphy using technetium Tc 99m-labeled albumin noninvasively visualizes lymph nodal and lymphatic channel abnormalities corresponding to the distribution of cutaneous lesions.[23] A skin biopsy specimen showing prominently dilated lymphatics has yielded on

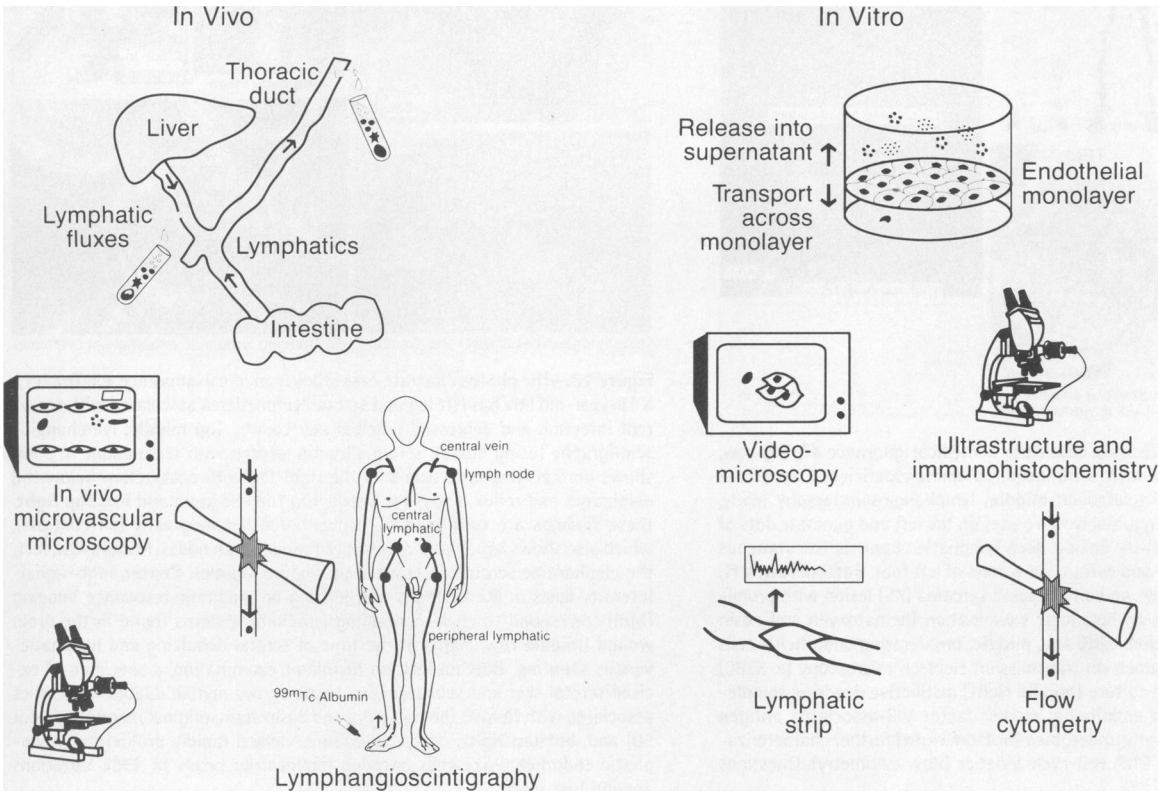

Figure 9.—Some in vivo and in vitro methods to investigate unanswered questions about normal and diseased lymphatic systems are depicted. See text for details.

long-term culture factor VIII-associated, antigen-positive, dendritic spindle-shaped cells resembling both lymphatic and blood vascular endothelium.[24] These cultured AIDS-Kaposi's sarcoma cells are being further characterized by flow cytometry, examined for retroviral and other viral DNA sequences by polymerase chain reaction, used in a hybridoma system to develop specific anti-Kaposi's sarcoma monoclonal antibodies, and subjected to angiostatic and angioinhibitory agents. As ignorance specialists, we wonder, what is the biologic link between the AIDS virus, immune dysregulation, and the lymphatic-derived Kaposi's sarcoma (type 1 ignorance question)? Can the process of angiogenesis and angiotumorigenesis be controlled or reversed with angiostatic-angioinhibitory agents or, alternatively, other modes of lymphatic-targeted therapy (type 2 ignorance question)? What are the societal implications of pursuing these questions, specifically as related to animal rights, human subject research, controlled trials, confidentiality, and cost-benefit ratios (type 3 ignorance question)?

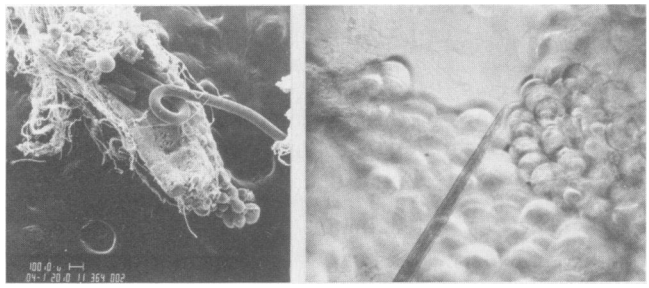

Figure 10.—The intralymphatic environment is recreated to probe ignorance about lymphatic filariasis. **Left,** a scanning electron-microscopic view shows an adult *Brugia malayi* emerging from an infected ferret lymphatic. **Right,** on day 72 of culture, a female *B malayi* is surrounded by microcarrier beads coated with human endothelial cells.

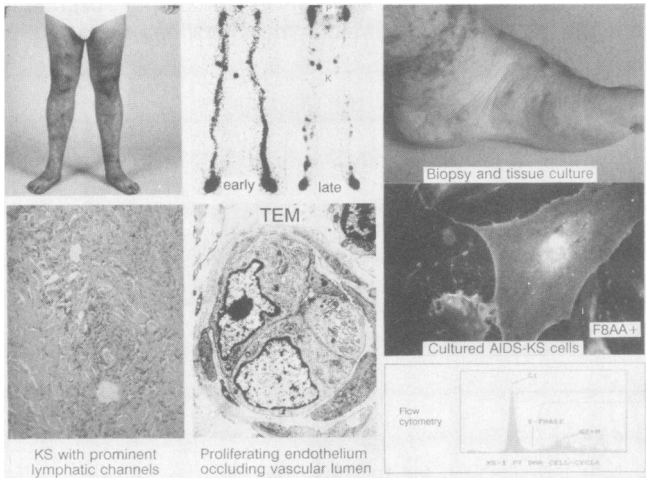

Figure 11.—The photos illustrate case study in medical ignorance #2: **Top row, left,** a 44-year-old gay man with acquired immunodeficiency syndrome (AIDS)-associated Kaposi's sarcoma; **middle,** lymphangioscintigraphy (early, late) shows hyperplastic inguinal lymph nodes on the left and punctate dots of persistent late tracer activity linking deep lymphatic channels to cutaneous lesions; and **right,** biopsy and culture were done of left foot. **Bottom row, left,** the biopsy specimen shows an early Kaposi's sarcoma (KS) lesion with prominent lymphatic channels on histologic examination (hematoxylin and eosin stain, original magnification × 86) and, **middle,** proliferating endothelial cells occluding the vascular lumen on transmission electron microscopy (× 3380) that yielded in long-term culture **(middle right)** distinctive dendritic spindle-shaped cells positive for endothelial marker factor VIII-associated antigen (F8AA+; × 200) and currently undergoing **(bottom right)** further characterization by such methods as DNA cell-cycle kinetics (flow cytometry). Questions abound (see text).

Finally, 20 years after our first case, another 15-year-old (Figure 12) presented to us with a similar picture of progressive, brawny, elephantine genital and lower extremity lymphedema of several years' duration, in this instance preceded and accompanied by recurrent local infection and low circulating T-helper cell counts ($\sim 2 \times 10^6$ per liter [400 per μl]). Lymphangioscintigraphy, confirmed by conventional lymphography, showed lymphatic blockade below the diaphragm with reflux into the pelvis, along with notable hypoplasia of retroperitoneal lymph nodes. Magnetic resonance imaging showed huge lymphatic lakes throughout the left leg and scrotum underlying cutaneous chylous vesicles. At the time of scrotal debulking and construction of a lymphatic venous bypass shunt in the edematous left groin, chyle welled up in the wound. Scrotal tissue showed extensive lymphangiectasia and intense fibrosis on histologic examination and yielded in tissue culture rapidly proliferating lymphatic-like endothelial cells. We ruminate, do these disorders represent a delayed onset of a genetic or congenital disturbance, or are they viral or even retroviral infections detectable by polymerase chain reaction, and does the process begin in lymphatic channels or in lymph nodes (type 1 ignorance questions)? What course of action is best when there is no good "standard" therapy available, are innova-

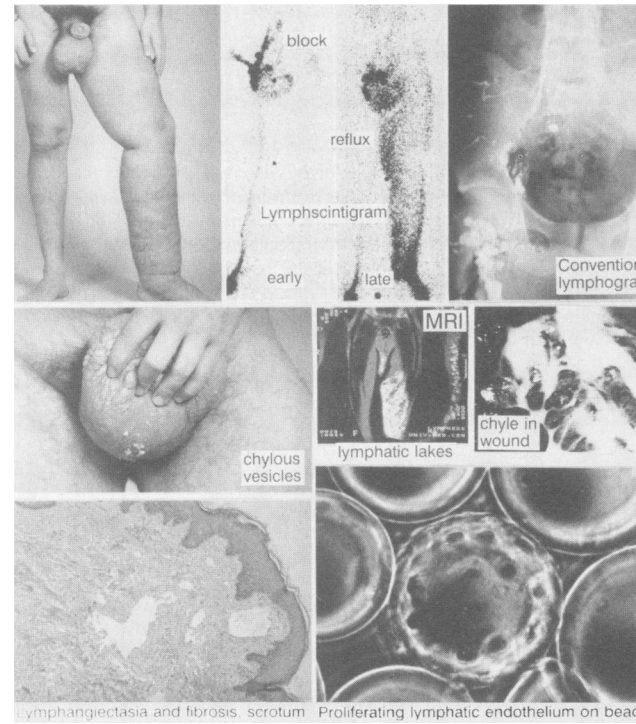

Figure 12.—The photos illustrate case study in medical ignorance #3: **Top left,** a 15-year-old boy has left leg and scrotal lymphedema associated with recurrent infection and depressed T-helper cell counts. **Top middle,** lymphangioscintigraphy (using human serum albumin labeled with technetium Tc 99m) shows normal lymphatic trunks in the right leg with obstruction below the diaphragm and reflux across the pelvis into the left groin and leg. **Top right,** these findings are confirmed by conventional lymphography (oil-contrast), which also shows hypoplasia of retroperitoneal lymph nodes. **Middle row, left,** the elephantine scrotum is covered by chylous vesicles. **Center,** high-signal-intensity lakes in the genitalia and left leg on magnetic resonance imaging (MRI) correspond to chyle-containing lymphatic cisterns found in the groin wound **(middle row, right)** at the time of scrotal debulking and lymphatic-venous shunting. **Bottom left,** on histologic examination, a specimen of excised scrotal skin and subcutaneous tissue shows myriad dilated lymphatics associated with fibrosis (hematoxylin and eosin stain, original magnification × 50) and, **bottom right,** on tissue culture, yielded rapidly proliferating, lymphatic endothelial-like cells covering microcarrier beads (× 495). Questions abound (see text).

tive operative approaches more prudent than the failed "conservative" standard of care, and how can efficacy be demonstrated (type 2 ignorance questions)? What are the social implications of unraveling the human genome, and how does one gain better understanding of the pathologic process with fetal research banned and the costs of managing rare "orphan" diseases spiraling (type 3 ignorance questions)? Once again, we are confronted with a lymphologic syndrome, manifesting the same constellation of swelling, scarring, immunodeficiency, vigorous angiogenesis, and potential nutritional depletion, to fill the "attic" of the brain and laboratory freezers with ponderables and imponderables for at least another two decades.

Thus, our personal odyssey in medical ignorance and swollen limbs has brought us to unimagined questions at the edge of the unknown. While sharing "late night thoughts" with Lewis Thomas and other renowned unknowers,[25] the uncluttered side of our mind fixes on a concluding insight in the final research report of one of our masterfully "ignorant" medical students:

I learned that if our projects seem easy and we surely understand them, we are not really probing deeply; it is only when we become perplexed by all the new discoveries unfolding before us that we can safely admit to being deep into the realm of research. . . . I truly gained an appreciation (and even a desire) for confusing and unexpected results. Not that I expected the unexpected, but rather I welcomed it when it came, and I eagerly probed to find out why it was unexpected and what it augured for the next set of experiments. . . . I cannot predict where I will be in medicine 20 years from now, but I like that. And I know the lessons of ignorance, creativity, and fortitude engendered in me by these seminars will keep me traveling a meandering path.[26]

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