

FOLLOW YOUR GUT

*The illustrious
career of
John G. Bartlett, MD*

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In every field of human endeavor there are a handful of persons whose names are synonymous with said endeavor. In English literature we think of Shakespeare. In physics we think of Einstein....In the field of infectious diseases the name John Bartlett is virtually synonymous with the discipline.

— Bennett Lorber, MD¹

John Bartlett (AQA, State University of New York, Upstate Medical University College of Medicine, 1962), is credited with discovering the etiological agent of antibiotic-associated colitis. He is a preeminent authority in human immunodeficiency virus (HIV), anaerobic pulmonary infections, community-acquired pneumonia, antibiotic resistance and bioterrorism through more than 500 original papers, 330 book chapters, and 14 books. A Master of the American College of Physicians, and member of the Institute of Medicine, he has received four career awards

from the Infectious Diseases Society of America. A true visionary, he continues to be an extraordinary investigator, clinician, and educator, even in his retirement years.

The early years

Born February 12, 1937, in Syracuse, NY, Bartlett grew up near the campus of Syracuse University, where his father helped found the Newhouse School of Journalism and served as Vice Chancellor. His family lived in a former fraternity house, where he had the entire third floor to himself. Bartlett kept himself busy during the long winters making “lots of stuff—all kinds of buildings and cars, even an electric scoreboard.”²

A gifted student at William Nottingham High School, he received numerous awards, served as the senior class president, and was voted most likely to succeed. He also was a talented athlete, and was the captain and quarterback of his high school football team. His days of football came to an abrupt end, however, when he suffered a concussion after being pummeled by Ned Weinheimer, a 230-pound lineman. Several years later, Weinheimer would become Bartlett’s brother-in-law.

After receiving a bachelor's degree in zoology from Dartmouth College in 1959, Bartlett returned to Syracuse to study medicine at State University of New York Upstate Medical Center. He completed his internship in internal medicine at the Peter Bent Brigham Hospital. The faculty mentors he admired most were cardiologists.

Bartlett's program director arranged for him to study at the University of Alabama in Birmingham under Dr. Tinsley Harrison (AQA, Johns Hopkins University, 1922), a world-renowned cardiologist and editor of the first five editions of *Harrison's Principles of Internal Medicine*. According to Bartlett, Harrison was a master clinician who made the residents "get down on their hands and knees so they could listen to heart tones, figure out the cardiac rhythm, and find the leaky valve."² Bartlett professes a love for his life in Alabama and for Harrison, whom he admired, but he said, "I did not love cardiology at all. There was something that just didn't fit very well for me."²

Although his foray into cardiology might have been a distraction, the move to Alabama was not a mistake. It was here that he met his wife, Jean Scott, a nurse on the medicine wards. They both cared for a 95-year-old patient, who, according to Bartlett, had "just about every disease you could think of—nobody thought he would ever get discharged."² After weeks of hospitalization, the patient improved dramatically. Elated by this turn of events, Bartlett turned to Jean and said, "This is a really incredible part of medicine to see this man, who was essentially moribund, now ready to go home. So why don't you and I go out and take him to dinner tonight?"²

Jean loved the date and the two were married a year-and-a-half later.

A foray into infectious diseases

Bartlett attributes his career choice of infectious diseases to the Berry Plan. Established in 1954, the Armed Forces Physicians' Appointment and Residency Consideration Program (Berry Plan) allowed physicians to defer military service while acquiring medical training in civilian institutions before fulfilling their two-year military obligation.³ When it was time for Bartlett to serve in the military, the Vietnam War was in full swing. As a captain in the Army, he was assigned to work in the emergency department



Bartlett, a freshman in college, with his father. Photo courtesy of Dr. Bartlett, from his personal collection

of the Third Field Hospital in Saigon from 1965 to 1967.

There was a steep learning curve in caring for acutely ill soldiers who were shot by enemy fire or had sustained penetrating wounds on the battlefield from punji sticks, which were used by the Viet Cong as a type of booby trap. Usually made of bamboo or wood, and sometimes rubbed with toxic plants, frogs, or feces, Punji sticks were designed to immobilize the enemy and produce infections of the feet and lower legs. Tetanus was a frequent complication from such wounds.

In addition to war-related wounds, Bartlett saw cases of typhoid fever and other tropical diseases. Although many of the patients were gravely ill when they were admitted, he was amazed at their rapid recovery thanks to newly available antibiotics and surgical management of wounds. Bartlett also enjoyed the special chemistry between internists and surgeons, and the sense of unity of purpose in the military. He recalls that outside the door to the emergency room hung a huge sign that read, "If you made it this far you have a 98.2 percent chance of making it back to the States."²

The investigator

Captivated by the ability to cure sick patients, Bartlett followed the advice of a senior physician at the Third Field Hospital who recommended that he study infectious diseases at the University of California Los Angeles Medical Center/Wadsworth Hospital under Dr. Sydney Finegold (AQA, University of Texas Medical Branch, 1949), a world expert in anaerobic infections.

Bartlett's early work described the clinical features of anaerobic pulmonary infections, and developed more sensitive approaches for bacterial diagnosis including percutaneous transtracheal aspiration, and quantitative culture of expectorated sputum.⁴ Bartlett made rounds with Finegold in the morning, worked in his lab all day, and then went to his house to translate. "A lot of the great literature on anaerobes from the turn of the century was written in French," explains Bartlett. "I spoke French and he didn't."²

Bartlett became a member of a self-proclaimed clique of anaerobic enthusiasts who tried to convince the rest of the field that *Bacteroides fragilis* was the cause of human anaerobic infections. Prior to this time, physicians and scientists disparagingly referred to the bacterium as

Bacteroides imaginalis. In 1972, Bartlett published in the *New England Journal of Medicine* that clindamycin was highly effective in treating clinical infections due to anaerobes, including *B. fragilis*.⁵

As his reputation in anaerobic research grew, Bartlett received a phone call from Sherwood Gorbach (AQA, Tufts University School of Medicine, 1962), who wanted to recruit him to Chicago. Bartlett was eager to work with Gorbach but considered it a dangerous career move since Cook County Hospital was featured in the newspapers every day as the site of some new scandal. Bartlett recalls that Gorbach told him, "Listen, Bartlett, when there's a nuclear holocaust, there will be two things left—cockroaches and Cook County Hospital."²

Gorbach was soon recruited to be chief of infectious diseases at the Los Angeles Sepulveda Veterans Administration (VA) Hospital, where Bartlett worked. Like Finegold, Gorbach was a flag-bearer of the anaerobic bandwagon at a time when many infectious disease experts still thought it was much ado about nothing. Although Bartlett's research was focused primarily on anaerobic lung infections, it was Gorbach who urged him to focus on the gut, since this is where "all the activity is."

At the time, clindamycin was a new drug promoted by the Upjohn Company for anaerobic infections. In the lab, Bartlett developed a hamster model of anaerobic infections and treated the animals with clindamycin. The hamsters treated with clindamycin always died of colitis within three days to five days. Similarly, in a clinical study by Dr. Francis J. Tedesco (AQA, Saint Louis University, 1968) et al., of 200 patients given clindamycin, 21 percent developed diarrhea and 10 percent developed colitis with pseudomembranes,⁶ prompting an FDA warning about this potentially life-threatening drug-related complication.

The colonic pathology of these antibiotic-treated hamsters matched that of a patient originally described as having "pseudodiphtheritic colitis" in 1893 by John M.T. Finney, a surgeon at Johns Hopkins Hospital. After the introduction of antibiotics by the mid-20th century, the number of cases of antibiotic-associated diarrhea with pseudomembranes in the colon increased. This disease entity was originally attributed to *Staphylococcus aureus* because *staphylococci* were frequently isolated from the stool of such patients. Oral vancomycin was an effective treatment. However, Koch's postulates could not be fulfilled, since *S. aureus* could not be isolated from all such cases, and pseudomembranous colitis could not be reproduced by inoculating *staphylococci* in animal models.

In 1975, Gorbach was recruited to Tufts New England Medical Center. Bartlett followed him there and set up his own lab at the local VA hospital to study the cause of what was then called clindamycin colitis. Bartlett's team found that concurrent administration of vancomycin with clindamycin provided protection to the hamsters, suggesting a gram-positive bacterial pathogen as the etiology.

Another clue came from the observation that direct inoculation of fecal contents from an infected hamster into human lung fibroblasts caused a cytopathogenic effect within four hours, suggesting the presence of a bacterial toxin.⁷ These effects could be prevented by giving an antitoxin raised in horses in the 1930s against the gas gangrene-causing bacterium, *Clostridium sordellii*. Bartlett's group then showed that the *Clostridium* toxin was sufficient to reproduce colitis in hamsters.⁸ The final step, representing a culmination of more than 400 experiments, came when his group found that a patient from California with antibiotic-associated colitis also had extremely high levels of this toxin in their stool. This seminal work was published in 1978 in the *New England Journal of Medicine*.⁹ Although the disease was originally ascribed to *C. sordellii*, Bartlett noted that neutralization of the bacterial toxin by *C. sordellii* antitoxin likely represents "antigenic cross-reactivity between clostridial toxins...but the weight of evidence strongly supports the pathogenic role of *C. difficile*."¹⁰

Now known as *C. difficile* antibiotic-associated diarrhea (CDAD), it is the primary bacterial cause of diarrhea in much of the developed world, and a significant cause of morbidity and mortality across hospitals and in the community. The cytopathogenic toxin assay used to discover the etiological agent, although expensive and difficult to perform routinely, remains the gold standard in many countries, including the United Kingdom.

In later years, Bartlett and Tedesco demonstrated that vancomycin is a highly effective treatment for patients with CDAD,¹¹ but clinical relapses may occur in up to 25 percent of treated cases.¹² Bartlett openly acknowledges the significant contributions of his research team, including Andrew Onderdonk, Te-Wen Chang, Sandra Willey, Nancy Taylor, and Ron Cisneros.¹³

The downside of working with hamsters, according to Bartlett, is that the lab members become attached to them. One technician loved a hamster so much that she wanted to take it home as a pet. Bartlett warned her that if she stopped giving the hamster vancomycin it would relapse with *C. difficile* colitis and die. "Well, she gave him vancomycin every day," says Bartlett, and the hamster lived over two years, which is the average life span of a hamster."²

The clinician and administrator

In 1980, Bartlett was recruited to the Johns Hopkins Hospital in Baltimore to serve as the Stanhope Bayne Jones Professor of Medicine, and Chief of Infectious Diseases.

In 1981, two reports were published in the *Morbidity and Mortality Weekly Report (MMWR)* describing a total of nine young homosexual men with pneumocystis, a rare form of pneumonia that afflicted transplant patients, and Kaposi sarcoma, an unusual systemic disease characterized by lesions of the skin, and gastrointestinal and respiratory tracts.^{14,15} By 1984, it was determined that HIV infection was the cause of the acquired immunodeficiency syndrome (AIDS), leading to progressive failure of the immune system and eventual death due to opportunistic infections and cancers.

Joel Gallant, one of Bartlett's trainees who became an international authority on HIV/AIDS, describes his former mentor as a "true visionary, who always knows what the next big thing will be, and embraces it long before it becomes the next big thing."² According to Gallant, "unlike the majority of infectious disease clinicians at the time, John Bartlett actually wanted to do something about AIDS."²

Bartlett recalls the story of one woman who was visibly distraught when she came to see him in the clinic. When he asked what was bothering her, she replied, "When I signed into register in the hospital, the person at the front desk asked me to put the pen down. She took up a Kleenex, picked up the pen and threw it into the waste paper basket. You know how that made me feel?"² This story, and many others like it, moved Bartlett to start an AIDS service, which was lacking in Baltimore and the surrounding region. At the time, there was only one other clinic serving AIDS patients in the nation—at San Francisco General Hospital.

As Bartlett recalls, many "people were afraid it was going to tarnish the Hopkins name,"² but the Chairman of the Department of Medicine Victor McKusick (AQA, Johns Hopkins University, 1962), was supportive of Bartlett's early efforts to recruit patients to Hopkins. Frank Polk, an infectious disease physician from Harvard, was recruited to Johns Hopkins in 1982, and like Bartlett, held a deep conviction that there should be a clinic dedicated to the care of patients with AIDS. The Johns Hopkins AIDS clinic opened in 1984 in the basement of the hospital, next door to McKusick's clinic for congenital dwarfism.

Under Bartlett's tenure as Chief of Infectious Diseases, the Johns Hopkins AIDS service was recognized as the second-best service in the country, after the one at San Francisco General Hospital. Bartlett was known to quip,



Bartlett, dressed as Santa Claus, making rounds on the inpatient HIV service during the holidays, circa 1980s. Photo courtesy of Dr. Bartlett, from his personal collection

"We're one earthquake away from being number one!"²

Bartlett attributes the success of the AIDS service to the extraordinary nurses, who "knew the disease, the patients, and the families—they ran the service."²

For many years, Bartlett attended on the inpatient AIDS service over the winter holidays so that other faculty could spend time with their families. He enjoyed dressing up as Santa Claus and handing out presents. One Christmas, he offered a wrapped present to a 65-year-old man who had tears in his eyes. When Bartlett asked him what was wrong, the man replied, "It's the first Christmas present I ever got in my life."²

Bartlett enjoyed caring for the forgotten patients with HIV, including the homeless, injection drug users, and inmates in the Baltimore prisons. According to Lisa Wolf, one of the original nurses on the AIDS service, "Dr. Bartlett's fame and full schedule could have limited his patient panel to the glitterati, but instead, it was full of men and ladies named Melvin, Joseph, and Annie, normal people from Baltimore's neighborhoods surrounding Johns Hopkins Hospital. They were poor folk, who bought their clothing from the same used clothing stores where Dr. Bartlett bought his ties and reading glasses."² A patient of Dr. Bartlett's for 18 years says of him, "Dr. Bartlett was the gold standard of doctors; not only did he know the medicines better than anyone—he took the time to get to know me personally. He was never judgmental and I felt comfortable telling him anything."²

When Bartlett became chief of the Johns Hopkins Division of Infectious Diseases in 1980, there were three

faculty members with a total research budget of less than \$285,000. By the time he stepped down in 2006, the division boasted 44 tenure-track faculty, an annual research budget of more than \$40 million, and internationally renowned research programs in HIV/AIDS, tuberculosis, viral hepatitis, sexually transmitted diseases, hospital epidemiology and infection control, antibiotic stewardship, enteric infection, and transplant/oncology infectious diseases. Most of these programs “sprang up from fellows trained under Bartlett and were inspired to remain in the division to tackle the next big thing in infectious diseases.”¹⁶

The academic leader and educator

As president of the Infectious Diseases Society of America (ISDA), Bartlett significantly shaped the direction of infectious diseases. Together with Anthony Fauci (AQA, Weill Cornell Medical College, 1965), a leading expert in HIV and the long-time director of the National Institute of Allergy and Infectious Diseases, Bartlett developed HIV treatment regimens as co-chair of the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents from 1996 to 2013.¹⁷

Bartlett’s *Medical Management of HIV Infection*, originally published in 1994 and now in its 18th edition, remains the definitive textbook on HIV clinical care. In addition to his effective writing style, which has been characterized as “cogent, persuasive, lucid, direct, and no nonsense,”¹ Bartlett has a unique ability to summarize and highlight important scientific and medical advances. According to Cynthia Sears (AQA, Sidney Kimmel Medical College, 1976), an expert in intestinal bacteria and their role in colon cancer, “I don’t know anyone who can synthesize and distill the clinical literature as well as John Bartlett.”²

Bennett Lorber (AQA, Lewis Katz School of Medicine at Temple University, 1980), an expert on listeriosis and anaerobic infections remarked, “Very few individuals become known as a world expert in a single area; John

is internationally recognized as a leader in at least six,” and he “has reinvented himself more times than the pop singer Madonna.”¹

Bartlett is also widely recognized as a leading figure in antimicrobial resistance, community-acquired pneumonia, and bioterrorism. His contributions to each of these fields are numerous, in the form of white papers, lectures, and advocacy, helping to change long-held prevailing perceptions, and illuminating the path forward. Together with the self-proclaimed Bartlett’s Renegades, David Gilbert (AQA, Oregon Health & Science University School of

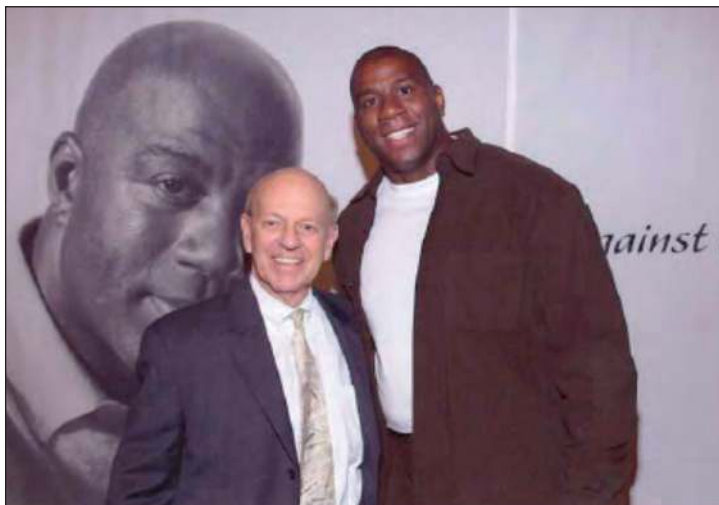
Medicine, 1963) and Brad Spellberg (AQA, David Geffen School of Medicine at University of California, Los Angeles, 1998),¹⁸ Bartlett outlined in an editorial in the *New England Journal of Medicine* a set of specific tasks to combat the worsening problem of antimicrobial resistance, shifting the focus from an impossible-to-win us versus them war on microbes to peaceful cohabitation.¹⁹

On September 13, 1997, at the annual IDSA meeting, Bartlett con-

vened the first ever symposium on bioterrorism to educate colleagues about biological weapons and emerging infections. On the heels of intelligence leaks about the Soviet Union’s biological warfare program, as well as the 1995 sarin and anthrax attacks in Tokyo by a Japanese religious cult, the symposium drew a standing-room-only audience of 2,500 clinicians.²⁰

The next year, together with D.A. Henderson, who is credited with the global eradication of smallpox, Bartlett started the Center for Civilian Biodefense Studies to implement and coordinate medical and public health responses to the emerging bioterrorism threat. He and his colleagues published a series of seven papers in *Journal of the American Medical Association* reviewing various biological warfare agents.

Bartlett’s “Game Changers” and “Hot Topics in ID” lectures, in which he summarized the most important findings of the preceding year in all areas of the discipline,



Bartlett pictured with Earvin “Magic” Johnson, Jr., at an event in the 1990s. According to Bartlett, “Magic did more to destigmatize HIV than anyone else.” Photo courtesy of Dr. Bartlett, from his personal collection

have been among the most highly attended sessions at the annual IDSA meeting. He enralls audiences by recounting fascinating stories and often injecting his talks with well-timed humor. When introducing the concept of fecal microbial transplantation by endoscopy as a method for treating *C. difficile* colitis at the didactic conference for infectious disease fellows, he concluded, “It looks like it really works, but the aesthetics suck!”²

The clinical fellows love rounding with him on the inpatient consult service because they are guaranteed to learn how to diagnose and treat a particular infection, as well as how the causative organism was named, and interesting anecdotes about the discovery of the latest antibiotic. Bartlett has unique access to these intriguing backstories because he reads the literature, and often calls the lead authors directly to obtain more information. He also has a knack for coming up with witty clinical pearls, which his students can still recite. To underscore the hierarchy of efficacy in antibiotics for treating *C. difficile* colitis, he would say, “Vancomycin for your mother; metronidazole for your mother-in-law.”² In addition to his legendary story-telling skills and acerbic humor, what captivates his audiences is his palpable excitement about the topic at hand, and his “sense of awe, his sense of wonder... kind of a gee-whiz

quality, a wide-eyed kid at the circus quality.”¹

Bartlett was one of the first to champion the use of the Internet for medical education, creating blogs and online forums to answer questions and generate discussion among HIV providers and patients. According to Gallant, his early espousal of new technologies for educational purposes was highly ironic since “this was a man who could barely turn on his computer.”²

Bartlett’s prodigious output in many diverse areas (his CV is more than 95 pages long and has a table of contents) has led his colleagues to laud his indefatigable work ethic.

One of his secrets is that he awakes every morning at 2 a.m., so that he can “get in at least five or six hours of work before the phone starts ringing or someone knocks at the door.”² He wastes little time, once traveling to China to give a one-hour lecture, only to immediately turn around and return to the airport. Although he occasionally may give the impression of the absent-minded professor—he was invited to give Grand Rounds once in Portland, Oregon, but mistakenly boarded the flight for Portland, Maine—any

downtime he has he spends writing, always equipped with a yellow legal pad and number-two pencil.

On more than a few occasions, Bartlett has been known to put his work above his health. His hospitalization for a herniated lumbar disc barely slowed him down, as he continued to keep all of his appointments from his hospital bed, and the infectious disease fellow would push him around on a gurney during rounds. One morning, he felt substernal chest pain while playing basketball with his son. He recognized the symptoms of angina but went on to give his scheduled Grand Rounds, and then continued working on a book chapter with an imminent deadline. It was only later in the afternoon, during a faculty meeting, that he mentioned his symptoms to the chief of cardiology. An electrocardiogram confirmed that he was having a myocardial infarction.

His wife, seeing a stack of papers under his arm as he was being admitted to the cardiac care unit, did not hesitate to tell the nurse, “I want you to snow him.”²

A kind, gregarious person

According to Fauci, “even though there are very few, if any, people in modern times who are world experts in as many areas of medicine, John Bartlett is one of the kindest, most gregarious people you will ever meet—he has a way of making everyone around him feel comfortable. He also has an amazingly positive outlook on life—for him,



Original oil painting by John G. Bartlett, MD, *Figures* (1980). The painting features a person suffering in the hands of a devoted, but helpless, caretaker. Photo courtesy of Dr. Bartlett, from his personal collection

life is a joy. He is a legend in the field of infectious diseases, but, above all, he is an outstanding human being.”²

Although his official retirement ceremony was held April 11, 2014,²¹ according to Bartlett’s wife, he “never retired—he just moved.”² They now live in Tupelo, Mississippi, near the birthplace of Elvis Presley. He still wakes up every morning at 2 a.m. and spends most of the day “on ID stuff—reviews, a few publications, lots of speeches on ID updates, guidelines, *UpToDate* edits and the NIH-funded Antibacterial Resistance Leadership Group.”² He is writing an article on the need for bright young physicians and scientists to combat emerging infectious diseases and the perennial problem of antimicrobial resistance.

Bartlett has been called a true polymath—a Renaissance man. One of his most beloved pastimes is painting. According to Finegold, “at one point during his training, he actually got tired and asked permission to go to Europe for a few months to paint and draw. He brought me back a beautiful still life.”²

Reflecting on his career, Bartlett admits, “A lot of my decisions were made without the idea that this is a really important part of my life or my career. But, of course, you often don’t know that at the time.”² When asked what advice he would give to the next generation of physician scientists, he offers, “Follow your passion, follow your gut—it might just lead you to the next big thing.”²

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