

**2011**  
**215<sup>th</sup> Annual Oration**

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**ORATION: That Which Endures: The Quiet Heroes of Medical Discovery**

Imagine this: you are five hours into a 13-hour flight from San Francisco to Sydney, Australia, but with soothing visions of the Great Barrier Reef, brilliant sunshine and immense blue seas, you are mellow indeed.

Your reveries dissolve, however, when the PA system crackles to life and a wavering voice asks, “Is there a doctor aboard?”

Confident of your abilities and perhaps inflated by that second glass of wine, you rise, scan the cabin, and, seeing a cluster of attendants at the back of the plane, stride quickly toward them. With your words “I’m a physician,” the crowd parts.

An ancient man huddles beneath several blankets, his head alone protruding above the black shroud. His skin is as white as the hair on his head, and his brow is stippled with sweat. His breathing is rapid and deep, his breath ominously fruity.

You nod a greeting and place your fingers on his neck. His skin is cold and clammy and his pulse is chaotic and feeble. Your warm touch rouses him, and he stares at you, his sunken eyes lit with confusion and fear.

You bend towards him, and as if on cue, galvanic chills lift the pitiable figure, seemingly intent on throwing him to the floor. You place a comforting hand on his quaking shoulder.

The man’s spasms seem to animate the stout woman seated to his right. After studying her companion, she frowns, shifts her gaze to you, and asks in a voice edged with challenge, “So, you’re a doctor?”

You compose your most professional expression and nod reassuringly.

“Good luck with this one,” the woman says with a snort. And before you can ask a question, she adds, “His doctor gave him an antibiotic for an infection in his prostate, but he didn’t take it...no, the genius didn’t even get the prescription filled...said the \$25 co-pay was too much...said it would cost less to get the drug in Australia.”

You nod with understanding.

“Did he take his insulin this morning?” she continues. “Who knows? And where are his needles and syringes?”

You shrug.

Shaking her head in disbelief, she says, “He put them in the checked bags...said he didn’t want security to think he was a drug addict.” Twisting in her seat with some effort and waving a finger at the shivering bundle, she adds, “Look at him: 83 and with hair growing out of his ears. Does he look like an addict to you?”

You shake your head in agreement. “No,” you say to yourself, “no addict here, just an elderly man with sepsis and diabetic ketoacidosis.”

In your mind’s eye you see with PowerPoint clarity the figures that explain to a molecular level the diseases rampaging before you. And you envision the therapeutic algorithms for treating each: the evidence-based plans for repulsing the malevolent, microscopic invaders and for halting the metabolic flood of acid and osmols. Then your gaze descends from your desperate patient to your empty hands. And your heart sinks.

You look right and left, hoping to spot another physician or, better yet, a nurse; a nurse is always the best solution to a difficult situation.

Alas, you are alone but for a flight attendant who appears much too young to understand the gravity of the situation.

The attendant leans towards you and whispers, “The Captain says we won’t be able to land anywhere for at least three hours.” Moving closer she adds, “One of the passengers gave me a bottle of nitroglycerin.”

You glance down at the brown bottle she cradles in her palm, and then at the pallid man whose pleading eyes transfix.

“So, what now doctor?” asks your patient’s companion, a quiver in her voice revealing a dawning panic. “What’s the plan?”

“The plan?” you ask yourself. “The plan? The plan is for me to parachute out of this plane.”

Then, inhaling deeply to steel yourself for what is to follow, you turn to the flight attendant and whisper, “Hold onto those nitros. I’ll be needing one myself before this is over.”

*The Lord hath created medicines out of the earth; and he that is wise will not abhor them.  
~Ecclesiasticus 38:4*

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Our power as physicians to prevent, control or cure disease flows from the merging streams of knowledge, training and experience and from our great reservoir of tests and therapies.

Each of us can describe where we acquired basic medical knowledge, post graduate training, and clinical seasoning, in part because the experiences of medical school, residency and clinical practice have been so powerful and immediate. And each of us can recall with appreciation the mentors who helped us merge medical knowledge with clinical skills to yield competency and perhaps even mastery.

What remains a mystery to most of us are the names and stories of those who have given us the tools to treat and cure our patients, tools which are the real source of our power as healers.

I suspect that as I was presenting the story of the elderly diabetic with sepsis and ketoacidosis, some of you envisioned the diagnostics and therapeutics you would order if he were your patient. But the topic for your consideration centers not on the things we might do to treat an illness, but rather on those men and women whose minds conceived and whose hands forged the tools of our trade, the tests and therapies we routinely employ to prevent or relieve suffering.

Allow me to present one story of medical discovery, a story of several men whose humble service gave us only a single medication, but a drug that over many decades has cured thousands of desperately ill human beings.

The 1940s had drawn to a close, and the country was turning its focus from the grim days of World War II to the future, which from American shores looked bright indeed. In the world of medicine, however, one threatening cloud darkened the horizon. That dark form, that fear, was that after only one decade, the antibiotic era might be coming to an end. Unthinkable, but penicillin, the miracle drug, appeared to be losing its power.

True, penicillin could still cure most patients with infections that only a few years earlier had been uniformly fatal: the young adult with viridans endocarditis, the post-partum female with streptococcal puerperal sepsis, and the child with pneumococcal or meningococcal meningitis. But in the late 1940s, strains of *Staphylococcus aureus* (at the time termed *Staphylococcus pyogenes*) resistant to penicillin had appeared in hospitals, and by the early 1950s, patients admitted with common infections such as pneumococcal pneumonia and cured with penicillin were becoming secondarily infected with *Staphylococcus aureus* and often dying of the superinfection. In 1950, Leslie Spink noted, “The incidence of strains of staphylococcus highly resistant to penicillin is increasing at an alarming rate.” He concluded, “...penicillin cannot be employed with a comfortable degree of confidence in the therapy of staphylococcus infections.”

To be sure, other antibiotics became available in the late 1940s and early 1950s. However, within months of the introduction of these agents, including streptomycin, aureomycin, terramycin and chloramphenicol, resistant strains of *Staphylococcus aureus* (and other bacteria) emerged in hospitals. Phyllis Roundtree and Edgar Thompson reported in 1952, “The new strains [resistant to penicillin and other antibiotics] have become well established in the hospital environment, both in the bedclothes and dust of the wards and in the noses of the nurses and doctors.”

Antimicrobial discovery in the 1940s and 1950s was not based on complicated biosynthetic processes nor, of course, on computer generated molecular models. No, the scientific approach to antibiotic development paralleled that which led to the introduction of penicillin.

In the 1870s, several observers reported that *Penicillium* mold found on oranges and jam produced a substance with antibacterial properties. In 1928, Alexander Fleming, a biologist, isolated the substance, which he labeled penicillin. Fourteen years later, in 1942, penicillin was first introduced into clinical use, and in 1944, the miracle drug became widely available.

Actinomycetes and streptomycetes, ubiquitous microbes present in soil and decaying vegetation (and sometimes termed “soil molds”), were quickly recognized as potential sources of novel antibacterial compounds. Thus, in 1945, tetracycline was isolated from a golden actinomycete by Benjamin Duggar, a retired botany professor working in Lederle Laboratories in New York. In 1947, chloramphenicol was recovered from an actinomycete by Gerald Langham, an agricultural geneticist working in Venezuela. And in 1952, erythromycin was isolated by Robert Bunch and James McQuire, biochemists working at Eli Lilly and Company in Indianapolis, from a streptomycete found in a soil sample from the Philippines.

In short, the Ecclesiasticus admonition that “He who is wise should not abhor medicines that come from the earth” was adopted with fervor by scientists of the era who coveted soil from exotic places, soil which might harbor microbes elaborating novel antibiotics.

One such scientist was Edmund Kornfeld (Figure 1), who received his PhD in chemistry from Harvard in 1944 and subsequently joined Eli Lilly and Company in Indianapolis. In 1951, Kornfeld wrote to a friend, the Reverend William Conley (Figure 2), a former U.S. Army chaplain with the 82<sup>nd</sup> Airborne Division who was a missionary in Borneo. Kornfeld explained Lilly’s botanical screening program and sent along several sterile vials. Within a month, Conley returned the vials with the comment, “I certainly hope there is something promising in our dirt out here, but if our attempts at gardening are any measure, I cannot say the prospects are promising.”

Kornfeld did not isolate a new antibiotic-producing organism from the original samples, and he sent Conley a second request and additional vials, urging the missionary to "...collect samples off the beaten track, away from towns and villages."

Conley was scheduled to leave Borneo on furlough and could not fill the new vials in a timely fashion. However, before departing, he asked a fellow missionary, William Bouw, to collect samples from a remote area of Borneo where he worked. Bouw consented and forwarded new samples to Indianapolis. In 1953, Kornfeld and his team isolated a previously unknown microbe, *Streptomyces orientalis*, which produced a unique compound designated 05856.

The *in vitro* properties of 05856 ~ the way the chemical behaved in the test tube ~ were remarkable: the antibiotic killed all staphylococci, including the penicillin-resistant strains causing havoc in hospitals. The drug's ability to inhibit staphylococci was very stable in pivotal serial passage assays, suggesting the agent might be clinically useful for a long period of time, a property lacking in penicillin, chloramphenicol, tetracycline and other available agents.

One of the early laboratory challenges confronting Kornfeld and his team was the difficulty in purifying compound 05865. The original purification method employed picric acid, a potentially explosive chemical, and as a result, an alternate process was developed. However, the new method yielded material with a purity of only 82% and when solubilized, produced a brown liquid aptly termed "Mississippi Mud." The impurities were to contribute to much of the toxicity forever associated with the agent. In any case, as the need was dire, the initial preparations were felt to be safe enough for use in humans.

The first human trials of compound 05865 occurred in the early 1950s and were quaint by contemporary standards. Richard S. Griffith (Figure 4), a physician and Eli Lilly clinical investigator, wrote, "The high specificity of the new antibiotic 05865 against staphylococci and relatively low toxicity in animals warranted clinical trial as soon as possible. We needed a patient..." As a result, house officers at several Indianapolis hospitals were asked to identify potential candidates. Dr. Griffith noted, "Many possible cases were seen. All were passed over because they were mild and would have healed themselves, because adequate therapy with other antibiotics had not been administered, or because the patient refused trial when told this was a new medication. Then one morning a surgical resident called and said, 'We have a patient for your new antibiotic.' This man had developed a severe infection of his foot following surgery. He had received large doses of all the available antibiotics, alone and in combination, systemically and topically, without improvement, and sensitivity studies showed that the staphylococci in his wound were resistant to all of these antibiotics. The foot and the lower leg were tremendously swollen and indurated, and there were several sinuses draining pus. The surgical staff recommended amputation. We told him about this new antibiotic and he said, just as any of us would have said, 'Anything that might save my foot.'

Because of the urgency of the case, we had to raise the dosage much more rapidly than we would have liked in order to get the therapeutic results as quickly as possible to save the man's foot. In five days he was getting 100 mg every eight hours and he felt better. Heat was disappearing out of his foot; his white cell count was dropping; and the exudate from his wound was less. During the next seven days the staphylococci disappeared from the wound, and his foot was free from signs of infection....Then we ran out of 05865. While we held our breath he continued to improve and two months later he left the hospital with an intact foot."

Because of such dramatic clinical results and the expectation that 05865 would vanquish staphylococcal disease, the drug was named vancomycin.

The medical community became aware of vancomycin when case vignettes like the one above were presented at national meetings. Dr. Griffith wrote, “After the 1955 Antibiotic Symposium, word soon got around that Lilly had an experimental antibiotic that looked promising against resistant staphylococci. We began to get appeals for help in desperate cases of staph infection that had not responded to other antibiotics ~ meningitis, pneumonia, septicemia and endocarditis. The telephone rang not only during the day but at night and during weekends.”

The need for the drug was so great that by 1956, vancomycin was being sent from Indianapolis to physicians throughout the country. “A lawyer’s 11 month-old baby was dying of staphylococcal meningitis in California,” reported Griffith. “The organism was resistant in the laboratory to all antibiotics, and three had been tried in combination with no response. Again came that call for help. The doctor was sent Vancocin. 500 mg were given into the jugular vein of this 11 month-old baby and were followed by a total of 1 gram over the next 36 hours. This brought about a dramatic cure.”

In 1958 vancomycin was approved for use by the FDA.

In the 1960s, other drugs with activity against penicillin-resistant *S. aureus* ~ methicillin in 1960 and cephalothin 1964 ~ became available, and the use of vancomycin fell, since the newer drugs had fewer side effects. However, with the emergence of methicillin-resistant *S. aureus* in the 1970s and with the recognition that the drug was effective in treating patients with *Clostridium difficile* colitis, the use of vancomycin surged. Now, more than fifty years after its introduction, vancomycin remains a potent weapon in our antimicrobial armamentarium.

With sound reason, their contemporaries and history have been kind to Alexander Fleming, who discovered penicillin, and to Earnest Chain and Howard Florey, who moved Fleming’s work from the realm of biological curiosity to that of clinical practice: all three were awarded the 1945 Nobel Prize for Physiology or Medicine “...for the discovery of penicillin and its curative effect in various infectious diseases,” and all three were knighted.

What of the compulsive chemist, Edmund Kornfeld, the generous missionaries, William Conley and William Bouw, and the physician-investigator, Richard Griffith? The public record offers only the smallest of glimpses into their lives.

Edmund Kornfeld worked for many years at Eli Lilly, where his scientific efforts led to a number of discoveries in the area of medicinal heterocyclic compounds. Like Conley and Bouw, Kornfeld held deep religious convictions and wrote on how he reconciled his religious beliefs with his scientific grounding. “Faith,” he suggested, “is neither irrational nor subrational, but in a wider sense it is perhaps superrational ~ above and beyond the confines of man-made logic.” He is alive and 91 years of age.

William Conley earned degrees in theology and anthropology and taught at several seminaries; he died in 2010 at age 93.

William Bouw and his wife, who was also a missionary, served in posts around the world; he died in 2006 at 88 years of age.

Richard Griffith also worked at Lilly for many years and participated in clinical studies that preceded the introduction of other novel antibiotics, including the first 1<sup>st</sup> generation cephalosporin ~ cephalothin ~ in the early 1960s, and the first 2<sup>nd</sup> generation agent ~ cefamandole ~ in the mid-1970s. He retired as a Professor of Medicine at the University of Indiana, and died in 1994 at 74 years of age.

One wonders if Kornfeld, Conley, Bouw, Griffith or their coworkers ever fully appreciated the everyday medical miracles they helped create. Similarly, one wonders if they

considered their roles in bringing vancomycin into existence an important accomplishment in their professional careers or merely a footnote.

William Conley, William Bouw and Richard Griffith have passed, and Edmund Kornfeld is quite elderly. Eli Lilly and Company no longer engages in antibiotic discovery or development. And vancomycin is being gradually supplanted by antibiotics developed specifically to treat patients infected with MRSA, *C. difficile* and vancomycin-resistant enterococci (VRE). Thus, under the hands of science and time, the greater and lesser stories of medical discovery are inexorably overlaid by newer and equally compelling narratives. So, what does endure?

What endures is the desire of men and women to play some role in the search for answers to vexing questions of human suffering. And because of what has been and what will be accomplished by so many nameless people propelled by simple good will, or scientific ardor, or even more self-serving impulses, most physicians rarely feel hopeless when confronting virulent disease or have the urge to bail out when faced by patients in dire need.

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