Walsh McDermott and Changing Conceptions of Tuberculosis Antibiotic Therapy: Latent Lessons for Health Care Reform

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Abstract

Although health care reform efforts are laudably directed at promoting quality and efficiency, added bureaucracy may have the unintended consequence of constraining physicians' creativity. This has the potential to undermine clinicians' freedom to reframe their thinking in response to unfolding biological knowledge, a defining feature of academic medicine. In this Perspective, the authors illustrate the confluence of creativity, context, and discovery through a historical example: the evolution of tuberculosis (TB) multidrug chemotherapy as espoused by Walsh McDermott and his colleagues during the 1940s and 1950s.

Before the discovery of streptomycin in 1943, clinician–researchers aimed to identify a “magic bullet” that would rapidly eradicate tubercle bacilli from the body. In the years following the discovery of streptomycin, it became clear that the biology of TB did not conform to researchers’ expectations. The recognition that treatment would neither be simple nor quick prompted further attempts to devise an optimal streptomyacin regimen, which would enable the host’s immune system to suppress infection and prevent the emergence of streptomycin-resistant strains. By the late 1950s, investigators clarified the limits of streptomycin’s effectiveness, which led to combined chemotherapy. In so doing, they gained a better understanding of drug–bacilli–host interactions and shifted attention from the host to the drug-resistant microbe.

The authors argue that this tale of discovery offers a latent lesson for academic medicine: As the health care system undergoes systemic restructuring, it is essential to preserve the freedom to reframe thinking and creatively solve translational problems in research and practice.

As academic health centers contend with health care reform, they may encounter a context of care that privileges bureaucracy over science. Rationales for care provision and payment, although intended to distinguish “wise from wasteful” spending, may be based on a thin evidentiary reed and have little basis in biology or medicine. Although reforms laudably seek to promote quality and efficiency, their unintended consequence could be constraining the creativity of physicians’ thinking about clinical problems—not by prohibiting experimental activities per se but, rather, by structuring a set of a priori principles and expectations that squelch the generation of hypotheses or promote premature closure. All of this has the potential to narrow the physician’s gaze during the clinical encounter.

Such a restrictive context, then, could undermine one of the defining features of academic medicine: the clinician’s freedom to reframe his or her thinking in response to biology. Every physician takes advantage of this liberty in daily practice as he or she assesses the natural history of a disease, observes the consequences of an intervention, and adjusts the therapeutic strategy to yield greater improvements. The physician exercises the same freedom in research, as he or she aims to elucidate new phenomena by creatively revising hypotheses, concepts, and experiments in response to unfolding facts. Introducing additional bureaucratic strictures, however, may distort the clinician’s thinking by limiting access to a care venue or resources, thereby hindering the pursuit of optimal care. Placing constraints on creative thinking may therefore threaten innovation and, ultimately, the vitality of academic health centers, which have long been celebrated as leaders of clinical advances.

History illustrates how critical clinical freedom is to innovation within academic health centers. In this Perspective, we will examine one nonlinear narrative in the evolution of tuberculosis (TB) antibiotic therapy which exemplifies how the reframing of clinical thinking in response to unfolding biological knowledge was essential to therapeutic progress. We will focus on the participation of Walsh McDermott and his group of clinical investigators at Cornell University Medical College and New York Hospital in research efforts leading to a successful TB chemotherapy regimen. Although McDermott’s contribution to this history is often connected to clinical trials with isoniazid (INH) on the Navajo Reservation in Arizona,1 his group played a pivotal role in the evolution of TB therapeutics, as evidenced by the archival record we reviewed at Weill Cornell Medical College.

Before clinician–researchers discovered streptomycin in 1943, they aimed to identify an antibiotic capable of quickly eradicating tubercle bacilli from the body. It became clear, however, that their expectations would not conform to reality. Animal studies of streptomycin proved that treatment for TB would be neither simple nor quick, a finding that
researchers soon confirmed in patients. This realization informed efforts to devise a streptomycin regimen that would enable the host’s immune system to both suppress the infection and prevent the emergence of resistant strains.

By the late 1950s, standard practice progressed to the administration of streptomycin alongside other agents for at least six months—a reframing of the medical community’s earlier expectations of finding a “magic bullet.” The advent of prolonged multidrug regimens responded to the adaptive capacities of bacilli. After contributing to these initial advances of the TB chemotherapy regimen, McDermott’s laboratory continued to have creative insights into the drug–bacilli–host relationship. Their work catalyzed a shift in attention from host to bacilli and promoted a framework that ran contrary to conventional thinking. Such freedom to reframe old ideas into new hypotheses is the hallmark of academic medicine, and it needs to be sustained in times of significant reform and organizational restructuring.

The Emerging Antibiotic Era

By the 1940s, the emergence of sulfa drugs, the proven effectiveness of penicillin, and the discovery of streptomycin gave the medical community hope that scientists could identify “magic bullets” for every conceivable microbe to eradicate pathogens from the body rapidly and simply.4 The ability to “intervene decisively in the course of a wide range of microbial diseases” led to a newfound confidence in medicine coupled with bacteriological research.5

Walsh McDermott was a witness to this revolution in medicine. He became a resident at Bellevue Hospital in 1934 just as modern medicine was coming of age5 and experienced some of these discoveries firsthand after contracting TB during his residency. Following a spell at the Trudeau Sanatorium in Saranac Lake, he returned to medicine with what his protegé David Rogers described as “a profound sense of wonder coupled with pride in science and medicine.”6 This awe inspired his work as the head of the Division of Infectious Diseases at Cornell–New York Hospital, a post he assumed in 1942. By 1944, McDermott began participating in research to elucidate the therapeutic application of streptomycin, an exciting new fungal agent with great potential for treating TB.7,8

Streptomycin garnered much enthusiasm because it was the first antibiotic to successfully influence the natural history of TB in vivo. It did not, however, meet the expectations of the medical community, which had hoped to find either a synthetic or natural antibiotic agent that could swiftly eradicate tubercle bacilli. In guinea pigs, it took six months of therapy to bring “the disease to a state of apparent arrest,” and evidence suggested eradication of bacilli in just 30% of the animals.9 The two researchers responsible for these initial findings, Corwin Hinshaw and William Feldman, established the general understanding of streptomycin’s therapeutic capacity. When writing about their discovery of streptomycin’s clinical effects on TB, they noted that the drug “did not appear to possess any rapidly curative action in tuberculosis, such as might resemble the therapeutic marvels achieved by several antibacterial drugs against some acute infectious diseases.”10

Indeed, streptomycin, which was thought to suppress tubercle bacilli growth, operated over several months as opposed to days.11 Although it was not the “ideal remedy for treatment of tuberculosis,” researchers still deemed the drug “remarkable” given that it was the only way to slow the progression of the lethal disease.9

The early toxicity studies conducted by McDermott’s group confirmed the merits of the new drug despite its limitations.12,13 McDermott “expressed the opinion that streptomycin exerts a definite action on the tuberculous process,” basing his claim on a small set of pulmonary TB subjects who experienced a complete remission or significant reduction in the size of cavities after at least two months of therapy.14 His group’s case reports of TB patients receiving the drug from 1946 to 1947 affirmed this “unprecedented ability”15: Previously, patients who suffered from rare forms of meningial or miliary TB typically died within a few weeks; when treated with streptomycin, however, they survived for several months. Patients with pulmonary TB, the form responsible for the majority of deaths, typically experienced a “prompt improvement of symptoms” and complete remission for at least several weeks of receiving streptomycin.16 By 1947, clinician–researchers accepted that streptomycin dramatically influenced the progression of the disease in the first few months of therapy and touted the antibiotic not as a cure but as a suppressive agent.16

Because streptomycin’s initial success did not mimic that of antibiotics used in the treatment of other acute bacterial diseases, it was difficult to establish the preliminary principles of administration. McDermott’s group speculated that any effective TB chemotherapy would need to suppress the bacilli over a prolonged period to facilitate the immune system’s contribution to producing a cure. Indeed, the prevailing goal of antimicrobial therapy in 1947 was “to establish control of an infection for a sufficiently long period to afford opportunity for the host to mobilize mechanisms for permanent control.”13 After contemplating “both the nature of tuberculous lesions and the poorly understood variables of the host–parasite relationship,” McDermott’s group concluded that “the ideal procedure in the chemotherapy of tuberculosis would be to administer the drug for many months.”17 This focus on how to facilitate the host’s response guided further research into the drug regimen.

To identify the optimal streptomycin regimen, McDermott’s group continued to experiment with the antibiotic. Their 1947 studies18,19 complemented the findings of more influential experiments funded by the U.S. National Institutes of Health and the American Trudeau Society and larger clinical trials performed by the British Medical Research Council from 1946 to 1948.14 The larger studies clearly supported the therapeutic value of streptomycin and advanced the randomized control trial design, but looking at the contributions of McDermott’s group offers a more nuanced understanding of the evolution of TB chemotherapy: It reveals how clinician–researchers shifted their focus from the biology of the host to that of the bacilli.

Early TB Therapeutics

McDermott’s group did not have much success identifying a streptomycin regimen which facilitated the host’s control over the infection. Their 1947 case studies observed that while most
patients showed definite signs of improvement within the first few months of therapy, many of those who suffered from chronic pulmonary or meningeal forms of TB experienced a recurrence of disease.\textsuperscript{11,17} Some patients relapsed during treatment, some relapsed after a purported treatment was concluded, and some, with severe damage or cavitation, continued to discharge the bacilli throughout therapy. These relapse patterns showed that streptomycin monotherapy was insufficient for a permanent recovery, but they did not yield much guidance on how to prevent reversal of the therapeutic effect.\textsuperscript{20}

McDermott and his group were not alone in this quest to find ways to best deploy the drug. In the first few years of streptomycin’s clinical use, the medical community found it challenging to gather facts about the drug’s window of effectiveness. Because “the natural history and clinical course” of TB varied from patient to patient, the prognosis was “often confounded,” and the impact of a particular treatment regimen was often unclear.\textsuperscript{21} The limitations of the existing medical technology compounded the confusion. In 1949, McDermott and a colleague acknowledged that clinicians could only identify the “beneficial effects of treatment” by assessing how “the course of the disease is altered.”\textsuperscript{22} Physicians relied on active surveillance, chest exams, chest roentgenograms, and sputum collection to track patients and the progression or regression of disease. McDermott and a colleague noted that these methods were insufficient for evaluating the efficacy of drugs like streptomycin, explaining that “the clinical evaluation of antituberculous agents will remain unsatisfactory until precise, quantitative criteria for measuring these changes are available.”\textsuperscript{22}

Drawing on their clinical experience with the failures of streptomycin monotherapy, McDermott’s group eventually helped identify streptomycin resistance as a more specific indicator of when patients would succumb to a fatal relapse of the disease.\textsuperscript{17} Their clinical work indicated that streptomycin-resistant strains appeared somewhere between 30 and 90 days into therapy.\textsuperscript{23} Yet, delivering streptomycin for periods of 45 days often resulted in more severe cases of TB after therapy ceased.\textsuperscript{24} The timing of the appearance of drug-resistant strains and of more serious infections led the group to question their goals for TB chemotherapy.

Though McDermott’s group initially intended to administer streptomycin for several months and thereby enhance the individual’s immune response, they found that monotherapy was not up to the task. They speculated that the continued use of streptomycin gave a survival advantage to resistant bacilli. On the basis of studies assessing how different doses of streptomycin influenced resistance patterns, McDermott and a colleague postulated that “[w]hen the survival of bacteria of an intermediate degree of resistance is prevented, the curve of antimicrobial activity would persist at a high level until sufficient time had elapsed for the relatively few highly resistant bacteria to multiply to predominance.”\textsuperscript{25}

The eventual multiplication of drug-resistant bacilli presented new challenges to the host’s immune responses. Infections that were “sufficiently prolonged because of general or local inefficiency in the patient’s defenses” enabled drug-resistant bacilli to turn into “the predominating member of the population.”\textsuperscript{26} McDermott recognized that prolonged monotherapy suppressed the infection, but did not give the host the opportunity to gain control over other drug-resistant bacilli which were able to survive and proliferate in this therapeutic ecosystem. This more complex understanding of therapy and resistance soon pervaded the thoughts of many investigators working on TB chemotherapy.

Given these realizations, by 1949 clinicians and researchers, including McDermott’s group, began to investigate combined multidrug regimens in which streptomycin was administered alongside other drugs to prevent resistance and thereby reduce new threats to a beleaguered host.\textsuperscript{27} McDermott and a colleague, for example, sought to evaluate whether para-aminosalicylic acid (PAS) and sulfones had an “ability to suppress the appearance of streptomycin-resistant bacilli.”\textsuperscript{22} Once the research community confirmed that this approach delayed the emergence of resistant strains in chronic pulmonary TB cases, a consensus emerged around 1952 that “long term combined streptomycin and PAS therapy could be confidently initiated.”\textsuperscript{27} This conclusion marked the beginning of further efforts to find other combination regimens that could prevent the emergence of drug-resistant bacilli.

**Theory Meets Biology**

The idea of combination therapy was based on the theory that there was a very low probability that a bacillus would evolve to be resistant to more than one drug.\textsuperscript{28} Although McDermott’s group was not a main player in promoting the use of triple-drug regimens, their work was instrumental in providing the clinical and theoretical justification to move beyond monotherapy.\textsuperscript{29} As already described, the Cornell group revised their initial hope that streptomycin would serve as a sole suppressive agent enabling the host’s immune system to defeat the infection. In addition, McDermott helped to popularize another drug, INH, and experimented with its delivery alongside streptomycin.

In 1949, McDermott and Hinshaw went to Germany to examine a promising new antimicrobial agent in the thiosemicarbazone series that had been used to treat TB in 7,000 patients. McDermott’s laboratory was one of three in the United States that sought to investigate this novel agent. All three teams played with various derivatives of nicotinic acid and ultimately developed INH, which entered clinical practice in 1952.\textsuperscript{30}

Although McDermott and others considered INH to be a candidate drug for monotherapy, because of its apparent superiority over streptomycin, this bias was countered by additional evidence suggesting that its deployment in combination therapy was a more successful approach.\textsuperscript{31–33} By 1965, several studies demonstrated that INH and a second drug like streptomycin or PAS could “produce uniformly satisfactory results.”\textsuperscript{34} These studies also indicated that the addition of a third drug might further inhibit the initial appearance of drug-resistant bacilli.\textsuperscript{34}

Part of the acceptance of this novel approach came from more knowledge of the adaptive capacities of tubercle bacilli. McDermott’s influential laboratory work on microbial persistence and latent infections gradually afforded researchers a deeper understanding of the drug–bacilli–host relationship. In 1956, contrary to
anyone’s expectations, McDermott’s team reported that drug-susceptible bacilli could persist in a latent state for months despite ongoing therapy with an effective agent or agents.36 On the basis of the observations from this experiment, in 1959 McDermott speculated that the bacilli possessed the ability to “suppress” any “metabolic functions” targeted by the drug, a state he termed “drug indifference.”36 As he reflected on this sort of bacillary hibernation, he reframed his thinking: “[P]erhaps we have been taking too one-sided a viewpoint in our preoccupation with the host mechanisms and should focus equal attention on this probably wide range of reversible changes on the part of the microbe.”36 This newfound focus on the reversible microbe also encouraged a more complex understanding of the sources of resistance and the correlative importance of prolonged multidrug regimens as a countermeasure.

Once McDermott and others began to pay greater attention to the adaptive behavior of bacilli, they assessed how antibiotics selected for such responses. In an article published in 1960, McDermott acknowledged the need for a prolonged multidrug chemotherapy—one lasting anywhere from 18 to 24 months—given that some bacilli outlasted the antibiotics’ initial therapeutic action.37 He observed that the drugs only eradicated the bacilli in the beginning of therapy, writing that “in all probability, for most of this period the chemotherapy is exerting only a protective or suppressive action, rather than the actual therapeutic action it exerts in the early months of therapy” and that it was “also clear that the bacilli are not eradicated from the host as a direct consequence of the chemotherapy at any time and are most certainly not eradicated within the first half-year of therapy.”37

In 1966, McDermott’s group published work on microbial persistence that offered further evidence for the limitations of prolonged therapy owing to the capabilities of the bacilli. Their experiments demonstrated that sterile bacilli could produce active disease in immune-compromised hosts.38,39 This finding emphasized the importance of the immune system in overcoming the infection—as McDermott and his colleagues had recognized earlier—and pointed to the formerly unrecognized therapeutic significance of the adaptive bacilli. Not only did this revised conception of TB respond to observations in the laboratory and clinic but, more fundamentally, it defied past expectations for TB chemotherapy. In sum, it was a mix of contrarian science.

Latent Lessons
Although the clinical landscape today is distinct from that of McDermott’s era, we believe this narrative offers an important lesson for individuals currently engaged in academic medicine: Having the freedom to reframe thinking in response to biology is instrumental for the delivery of innovative care at the borders of knowledge. Indeed, McDermott’s group contributed to advances in TB chemotherapy because they could revise their thinking in response to new clarifications in the disease’s trajectory, and ask probing and contrarian research questions. Once it became apparent that streptomycin would not quickly eradicate TB, McDermott’s group sought to find a prolonged monotherapy that would facilitate the immune response of the host. The appearance of streptomycin-resistant strains, however, led them to shift their goal to circumventing the adaptive mutability of the microbe. In response, McDermott and other clinician–researchers aimed to identify a successful multidrug regimen by the late 1950s. McDermott also contributed creative insights into the drug–host–bacilli relationship, namely on latent infections, that supported additional refinement of combined chemotherapy regimens.

The many turns in this history of discovery point to the need for systems of care that can accommodate developments which may run counter to a priori expectations, particularly when those assumptions are linked to funding streams or care structures. Imagine if McDermott and his colleagues had discovered that treatment for TB took longer than for conventional bronchial infections and required multiple drugs against the backdrop of stringent utilization review and parsimonious formularies. Restrictions on length of stay and medications could have resulted.

This example seems far-fetched only because we know the biology of TB and the value of combination therapy over a prolonged period. But what of the corners of medicine where we do not yet know the biology of a disease or its time course for treatment? Will physician–scientists continue to have the freedom to engage in the translational work that predates formal studies and is predicated on observation and contemplation? Efforts to increase efficiency under health care reform could imperil that liberty, which is so essential to medical creativity, and could damage academic health centers’ role in innovation.

For in academic health centers, physicians practice medicine amidst uncertainty that requires them to revise their thinking as knowledge unfolds, just as McDermott and his colleagues did over 50 years ago. And McDermott’s legacy continues to this day: His research on microbial persistence remains relevant to defining the current norms of TB therapy. Today’s experts, alarmed by the continued rise in multi-drug-resistant infections, are now advocating for the discovery of antibiotics that target sterile bacilli.40 The continued significance of McDermott’s work indicates how central the evolving conceptualization of disease is to finding novel remedies, and how it requires the contributions of academic medicine over a term longer than a fiscal year or a market cycle. We remain the beneficiaries of discoveries made more than a half-century ago that are only now coming into a period of active investigation, again in academic health centers. The symmetry is inescapable: an iterative process of discovery over generations, all sheltered by the freedom of inquiry made possible by academic health centers.

If academic medicine is expected to maintain such efforts for generations hence, clinician–researchers must be able to test ideas that run counter to prevailing thinking and to efficiency models that reflect only what we think we know, not what is yet to be understood. In the existing climate of systemic health care reform, it is essential that we preserve the intellectual freedom that will allow McDermott’s heirs to continue their important work.

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