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PERSONAL EXPERIENCE

From Bed to Bench to Bed — and Beyond

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"From Bed to Bench to Bed" is a phrase used so often as to risk becoming a cliché. Yet it is in fact a dictate that can guide us to the amelioration of human suffering on a global scale. Translated into the words of Richard Lockshin in his lead editorial for this *Journal*, the first half of the phrase asks, "What phenomena do clinicians observe that are crying for the attention of laboratory researchers?" And the second half asks how these laboratory researchers can uncover "important cellular and molecular mechanisms that lead to new approaches to clinical control."

These principles of "Bed to Bench to Bed" may be most vividly exemplified by telling a story. This is the story of a "Bed to Bench to Bed" cycle that took place over 32 months in the 1960s on the Indian Subcontinent. By today, it has already saved an estimated 50 million lives. It is the story of oral rehydration therapy for cholera.

Cholera is an acute diarrheal disease that has plagued the world at least since the first Asiatic pandemic of 1817. Though permanently endemic in Asia, it has caused epidemics in Europe and America (resulting in the deaths of U.S. Presidents James Polk and perhaps Zachary Taylor), and it rages even today in Zimbabwe. In 1854, John Snow established the link between cholera and contaminated water in London. That same year, the Italian physician and pathologist, Filippo Pacini, identified the causative Vibrio bacillus, rediscovered 30 years later by Robert Koch.

But as recently as 1965, little was known of the mechanisms by which the cholera exotoxin elicited the profuse diarrhea that dehydrated millions of people every year and propelled so many of them into shock and ultimately to their death. This critical question had arisen at the "bed" but had not yet been answered at the "bench." The prevailing theory at that time was that the toxin somehow poisoned the sodium pump that actively transported salt and water out of the intestinal lumen back into the circulation, thus preventing the reabsorption of any fluids from the gut.

In 1965, I first arrived at the Pakistan-SEATO Cholera Research Laboratory (later the International Centre for Diarrheal Disease Research, Bangladesh, or ICCDRB) in Dacca, East Pakistan (now Dhaka, Bangladesh), for a two-year tour of duty as a freshly-minted officer in the U.S. Public Health Service. Just then, the Director of the NIH Clinical Research Center, the late Dr. Robert Gordon, was visiting the facility. He surmised that inactivation of the intestinal sodium pump should theoretically result in a net positive shift of electric potential in the lumen, and so he suggested that we find a way of measuring this electric potential in the human patient in order to test the still unproven sodium pump hypothesis.

The Director of the Laboratory, a physician and U.S. Navy Captain, Robert Phillips, had already had extensive experience with cholera in the Philippines and had made early but unsuccessful

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attempts to counter the dehydration of the disease with oral solutions. He had established professional contacts with many of the world's most eminent physiologists and he arranged for me to visit the laboratory of Professor Hans Ussing (inventor of the ubiquitous Ussing chamber for every variety of membrane transport research) at the Institute for Biological Chemistry in Copenhagen.

After a couple of months in Ussing's laboratory, I had devised a method to measure transmural electric potential in the intact human intestine, using KCl-agar vinyl tubing that was swallowed and passed into the small bowel as an electrical probe. A similar tube was planted on the abraded skin of the forearm as a reference electrode. The electric potential between the tips of the two tubes was measured by a standard pH meter. This work was all done at the "bench" in Copenhagen.

Now it was time to return to Dhaka and take this new technique from the bench back to the bed. I and my associates—James Taylor and Jnan Saha—did exactly that with a number of Bengali patients who had acute and then convalescent cholera. Although Captain Phillips, when in Manila, had previously tried to use glucose in oral solutions to "drive" the fluid out of patients' intestines back into their blood stream, it might not have occurred to us to introduce glucose into our test solutions in our research patients had it not been for another lesson from the "bench."

Browsing in the library of the Cholera Laboratory one day, I came across an article from the Physiology Laboratory at the University of Sheffield, England, which showed an increase in transmural electric potential when glucose was infused into the rabbit ileum in vivo. I decided to try adding glucose to the perfusion solution in our patients to "test" our novel measuring system. It worked. The intraluminal charge in all our subjects, even during the height of acute cholera, became much more highly negative as soon as the glucose was introduced (1).

It immediately came as a brilliant inspiration to our Chief of Clinical Research at the Cholera Laboratory, Dr. Norbert Hirschhorn, that this demonstration of an intact active sodium transport pump in the intestine had enormous implications for the therapeutic potential of oral rehydration solutions containing glucose as well as the electrolytes being lost in the diarrheal fluid. Hirschorn promptly spearheaded an effort to use glucose-containing electrolyte solution for rehydration of cholera patients under closely-monitored metabolic ward-type conditions. Again, it worked. The results were reported by Hirschhorn et al. in 1968 in a landmark paper in the New England Journal of Medicine (2).

The "bed-to-bench-to-bed" cycle had almost been completed. But the latter bed was in a research ward setting, not in regular hospital conditions. This next step in the cycle was completed by David Nalin and Richard Cash when they came to Dhaka in 1967. They and their colleagues treated 29 consecutive patients almost exclusively with oral rehydration solution, and the results were spectacular. All 29 patients recovered completely with an 80% reduction in the need for intravenous fluid replacement (3). The stage was now set for a stunning revolution in public health practice worldwide. But the drama needed one more act to reach its finale.

It had yet to be shown that oral rehydration therapy (now universally known by the acronym, ORT) would work outside of health care facilities, in rural villages where cholera was most endemic. Once again, Nalin and Cash led the way. With the help of local physicians, the encouragement of the Laboratory's Chief of Epidemiology, Dr. W. Henry Mosley, and the cooperation of American officers from the Center for Disease Control (CDC), they demonstrated the effectiveness of ORT in 580 patients treated at a primitive outpost in the rural village of Matlab (4).

Now the cycle was not only complete, but extended. It had gone "From Bed to Bench to

Bed," but it had then taken one more crucial step—to the "Field"—for ultimate validation as a public health breakthrough with—again to quote Dr. Lockshin's editorial—"implication on a global scale."

This story is just one among many that demonstrate the process of taking a clinical question from the bed to the bench, carrying the answer from the bench back to the bed, and then extending the benefits to the field—to the wider world. This is the process that Dr. Lockshin has described and the mission to which the *Iranian Journal of Gastroenterology and Hepatology* is so nobly committed.

Yet beyond general and frankly well-worn lessons about the clinical applications of basic research, this story has at least two specific implications for Iran and its neighbors. First and most obviously, there have been repeated fatal outbreaks of cholera in Iran since the 19th century—most recently in 1998 and 2005 and again in Qom and Karaj in August of 2008. Hence, whatever insights and treatments have been developed as an outgrowth of research over the past 40 years have direct applicability to this country and this region.

Equally important for Iran, though, is the principle that successful clinical and translational research requires that *science goes where the disease is.* We learned that lesson when we studied cholera in Bangladesh, *where the disease was*, not at Harvard Medical School or the NIH. We continue to learn that lesson every day at my own institution, Mount Sinai School of Medicine, where our unique expertise in Crohn's disease, for example, arises largely from the fact that there are tens of thousands of patients with that disorder in our immediate vicinity who beat a path to our doors.

Yes, of course we have done some basic research on cholera in America (5), just as important clinical studies on inflammatory bowel disease (IBD) have been done in Tehran (6). The fact remains, however, that in science as in life, we should play to our strengths. Although from Tehran alone there have been about a dozen meritorious publications over the past 30 years concerning IBD, Iranian medicine has been infinitely and appropriately more productive with scores of papers on Behçet's disease (7-9) and hundreds more on hepatitis (10-12) and diarrheal disease (13-15).

With the input of so many talented physicians and other scientists from Iran and its neighbors, we can expect that the *Iranian Journal of Gastroenterology and Hepatology*, under the guidance of Richard Lockshin and his associates, will fulfill the twin missions of solving clinical problems with laboratory and clinical research, and turning those solutions to the benefit of their own citizens as well as others throughout the world.

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