A Physician-Scientist’s Tale

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... at the Tabard as I lay
Reedy to wenden on my pilgrymage
To Canterbury with ful devout corage,
At nght was come into that hostelrye
Well nyne and twenty in a compaignye,
On sondry folk, by aventure yfalle
In felaweshipe, and pilgrims wren they alle.
—Chaucer, The Canterbury Tales

Supper was over and we were just lounging. A hearty meal had capped a day of exciting scientific sessions. But what to do next? The meeting place was out in the country, far beyond city lights. It was too early for bed, too dark for a stroll, and there was no particular place to go. Each person at the table took a turn at stoking the conversation. We were running out of topics and spontaneity.

Suddenly, the animated voice of the host, who was seated at our table: each person would tell the tale of how he or she got started in research. What were the circumstances? The motivation? How easy the first passage? The lessons?

New life at our table. The two seated closest to the host told their tales. The following was my story.

As my medical residency was drawing to a close, I was summoned to the chairman’s office. As a rule, this sort of invitation presaged either an admonition, a fresh assignment, or, uncommonly, a reprimand. The chief, Dr. Snapper, was a professor of the old school, a Hollander by birth and Germanic by training. He was well known internationally for his studies of metabolic bone disease and was highly regarded for his clinical skills.

Dr. Snapper was in a congenial mood. His friend in Holland, Dr. Wilhelm Kolff, had invented an artificial kidney. This kidney had been tried in a few instances of

uremia and seemed to hold promise as a last resort in acute renal failure. Dr. Kolff had offered to send one of his machines to our hospital for testing. Dr. Snapper thought that I was the ideal person to take on this assignment because I was on the verge of completing my medical residency and about to begin one year of pathology. What would be more natural than having the former chief medical resident responsible for the medical management of patients in acute renal failure, use the artificial kidney when medical management proved ineffective, and do the autopsy in his role as resident in pathology if things did not turn out well?

The apparatus arrived a few weeks after our meeting (Fig. 1). In essence, it consisted of a large, unwieldy bathtub on which was mounted a rotating drum. The dialysis membrane was sausage casing that was wound around the drum in a continuous spiral; at each end the casing was connected to a special rotating joint that enabled the casing to remain untangled while the drum continued to revolve. The sausage casing was obtained from a meat-packing house in Chicago and had to be thoroughly rinsed before use. Gallons and gallons of bath fluid had to be prepared fresh for each patient in accord with the individual’s uremic state and electrolyte imbalance. By the time the apparatus arrived, Dr. Snapper had put together a team of two urologists and one cardiac fellow to assist me in the placement of arterial and venous catheters and to participate in the round-the-clock monitoring of the patient during dialysis.

No member of the team had any formal training in science, and none had previously engaged in this type of invasive human experimentation.

Unbelievably, the apparatus did work. Lives were saved. In the course of managing patients who were expected to be candidates for the artificial kidney, we also learned a great deal about the management of acute renal insufficiency. Indeed, by the time I had finished my year in pathology, we had established the efficacy of the artificial kidney, written several papers about both the management of acute renal insufficiency and the application of the artificial kidney, and Life magazine had featured our research in one of its issues. We also received visitors from other institutions. Among them were physicians from the Peter Bent Brigham Hospital, who, impressed with our results, returned home to build a better model, which, in turn set the stage for modern renal dialysis.

This heady experience with the artificial kidney also had a sobering aspect. My understanding of research on the kidney and in hemodynamics was sorely inadequate. To remedy this deficiency, I obtained a research fellowship from the American Heart Association. I was to spend 6 months in Homer Smith’s laboratory at New York University, and 6 months in the Cournand–Richards laboratory at Bellevue Hospital (Fig. 2). Little did I expect that this year would lead to a 5-year term as an established investigator of the American Heart Association. But that is another story. Here I will deal with only the 6 months in the Cournand-
Richards laboratory, which played a critical role in shaping my lifelong career in research.

My first encounter with Cournand did not augur well. I showed up at Bellevue Hospital well before the appointed hour. To escape the crowds milling aimlessly in the lobby, I took the stairs to the first floor where the Cournand-Richards laboratory was presumably housed. The stairs emptied onto a long corridor with windows on one side and closed heavy doors on the other. No one was in sight. I walked down the corridor looking for an open door. Finally I found two in a row: the first was clearly a secretarial office, but no one was there. I moved on to the next open door. Success. There, in the far corner, was Dr. Cournand himself. I recognized him immediately, even though I had only seen him once before, from afar, in a large lecture hall. He sat on the edge of his chair at a large desk in the far corner near the window, totally immersed in the papers on his desktop and completely unaware of my presence in his doorway. I still remember the room. Everything about it was gray—even the light that filtered in through the unwashed window. His desk faced one wall; behind his back were tall green-gray files crowned with heaps of books and papers in calculated disarray. Even now I think of his office as a prison cell without bars.

Instinct told me that I could not have arrived at a worse time. However, my reflexes were too slow. Before I could retreat, Cournand sensed my presence and turned quickly to face me. (I learned later that his practice was to leave his office door open in case some procedure or test in one of the adjacent rooms called for his immediate attention.) Half out of his chair, looking directly at me, he challenged, "What do you want? Where's Ruth?"

"My name is Fishman."

No response. Arrested in midair, he stared at me, clearly upset at being disturbed.

I continued lamely, "I am from the
American Heart Association. I am scheduled to work with you during the coming year.”

No response.

By now, he was standing. A pause. “You must be mistaken. I am not expecting any trainees. You probably want Stan Bradley.” (I had never met Dr. Bradley, but I knew of his research on the liver at the Columbia-Presbyterian Medical Center—at the opposite end of New York City.)

It was a standoff. He was ready to turn back to his writing. I had no choice but to leave. Suddenly a new actor appeared on stage. A young, attractive woman stood behind me, in the way of my retreat.

She spoke past me, over my shoulder, directly to Cournand. “He is right. You and Dr. Richards did accept him. The letter is on my desk. I have set up a desk for him in my office.”

Cournand did not turn a hair. He simply shrugged, sank back into his chair, and went back to his writing. It was Ruth who beckoned me to follow her to her office next door. This was to be my headquarters in the months ahead.

For weeks thereafter, Cournand was civil but disinterested. Left to my own devices, I explored the laboratory and met the members of the two teams: one was devoted primarily to cardiac catheterization and heart failure; the other to gas exchange. Each team was run by distinguished investigators, but each team had all the hands it needed. I was welcome to watch, to ask questions, to learn techniques, and occasionally to lend a hand. But I was clearly an observer. In my spare time I attended conferences and made ward rounds with J. Burns Amberson and Julia Jones. Every now and then I visited with Dickinson Richards. But, I did not belong.

Tired of reading and bored with the aimless mastering of analytic techniques and recording machines, I turned to the old data books in the blood gas laboratory. All samples of blood and gas were done in duplicate on separate machines—and redone immediately if any inconsistency was found. The books were carefully guarded by Mrs. Lester. Every now and then, in the course of a cardiac catheterization, Cournand would dash in, study the results, and order repeats if there were any question about any of the data. It was in these old data books that I found the roots of my future research on the pulmonary circulation.

Before proceeding, let me remind the reader of the state of understanding of the pulmonary circulation in the 1950s. In 1946, von Euler and Liljestrand had published their seminal paper on the effects of the respiratory gases on the pulmonary circulation of the open-chest cat. They showed that acute hypoxia (and hypercapnia) raised pulmonary arterial pressure.1 They measured neither cardiac output nor pH. However, they reasoned with powerful insight that acute hypoxia was a potent pulmonary vasconstrictor and that it was a mechanism by which local alveolar hypoxia would automatically adjust local blood flow to local ventilation.

A word is also in order about the state of determination of cardiac output at that time. Estimates of the cardiac output in humans were both indirect and inaccurate. The Fick principle had been published long ago in the brief proceedings of the Würzburg Physikalische-Medizinische Gesellschaft for July 9, 1870.8 The communication went as follows:

Herr Fick has a contribution on the measurement of the amount of blood ejected by the ventricle of the heart with each systole, a quantity the knowledge of which is certainly of great importance.—It is surprising that no one has arrived at the following procedure by which this important value is available by direct de-
termination, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time, and how much CO₂ it gives off. One takes during this time a sample of arterial and a sample of venous blood; in both samples oxygen content and CO₂ content are measured. The difference of oxygen content gives the amount of oxygen each cubic centimeter of blood takes up in its passage through the lungs; and as one knows how much total oxygen has been taken up in given time, one can calculate how many cubic centimeters of blood have passed through the lungs in this time, or if one divides by the number of heartbeats during this time, how many cubic centimeters of blood are ejected with each beat.

Since for the demonstration of this method two gas pumps are needed, your reporter unfortunately is not in a position to communicate experimental data.

Having enunciated the concept, Fick undertook no experimental proof. Stating the principle was an end in itself. Eighteen years after his short communication, Grehan and Quinquaud applied the principle to the determination of cardiac output in dogs, followed in a few years by a more detailed study of the cardiac output in the horse. The arteriovenous oxygen difference in humans was not yet known. Indeed, not until the late 1930s did Courand and Richards resort to right-heart catheterization for the sake of obtaining samples of mixed venous blood for the determination of the cardiac output in humans (Fig. 3). When I came into the Courand-Richards laboratory, the Fick principle was in the air.

Having developed the technique of right-heart catheterization for physiologic studies in intact, unanesthetized human subjects, it was natural for the Courand-Richards laboratory to extend the observations of von Euler and Liljestrand on open-chest cats by adding determinations of cardiac output. Motley et al. reproduced the pressor effect in normal human volunteers by administering an inspired mixture containing 10% oxygen and nitrogen. The test gas was administered for 10 minutes before blood and gas samples were drawn for the determination of the cardiac output by the Fick principle. Their paper, based on five human subjects, was published in the American Journal of Physiology. One reviewer, Dr. Wallace Fenn, while recommending publication, expressed surprise in his cover letter at the finding that cardiac output decreased during acute hypoxia. To him, this decrease made no sense physiologically.

On reviewing the results of these ex-
periments in Mrs. Lester's data books, I was impressed by the tendency of the values for the respiratory exchange ratios to be lower during hypoxia than during ambient air breathing. My attention was drawn to the respiratory exchange ratios, because recent research from Fenn's own laboratory had pointed out that when low oxygen mixtures were inspired, it might take a long while to reach a steady state of respiration and circulation. Failure to achieve a steady state would be reflected in a low value for the respiratory exchange ratio, leading in turn to a low value for oxygen uptake (the numerator of the Fick equation). If one recalculated the data of Motley et al. assuming that oxygen uptake during hypoxia remained unchanged rather than decreased, cardiac output turned out to be either normal or increased, as Fenn had anticipated.

I showed my calculations to Cournand. He was annoyed. He recalculated the data. He ran back and forth between his office and the blood gas laboratory, checking numbers. Finally, he was convinced. I was told to present the results at the Saturday morning conference. This was the test. At the conference, all agreed that although the paper by Motley et al. had confirmed the pulmonary pressor effect of acute hypoxia, the values for cardiac output seemed to have been unduly low because of a lack of a "steady state." The 10 min exposure to 10% O\textsubscript{2} had simply been too brief for oxygen uptake, measured at the mouth, to reflect accurately the oxygen uptake by blood coursing through the lungs and by systemic tissues and organs. A new set of experiments were to be undertaken with milder degrees of acute hypoxia and, if necessary, using the respiratory exchange ratios as a guide for longer periods of equilibration.

These observations on the effects of acute hypoxia marked the beginning of my acceptance as an active player in the laboratory. Moreover, Cournand and Richards became interested in having me acquire additional training in hemodynamics and respiratory physiology. In the laboratory they encouraged my interplay with Aaron Himmelstein, a thoracic surgeon, who was extraordinarily adept at cardiac catheterization and bronchospirometry. In time, the association with Himmelstein and with Fritts was to lead to further applications of the Fick principle, including the measurement of blood flow through each lung separately during acute hypoxia, the determination (Fig. 4) of pulmonary collateral blood flow in humans, and to a succession of attempts to unravel the mechanisms responsible for the hypoxic pressor effect.

![Figure 4. The "effective" pulmonary collateral blood flow in man. (Reproduced from Fig. 1, ref. 7.)](image_url)

Tales of this sort generally have a moral. Chaucer's pilgrims often concluded their narratives with timeless lessons, such as "success often occurs in the face of adversity," "the universe is directed so that everything happens for the best," or "what must be should not only be tolerated, but also celebrated." One can add others: "one person's oversight can begin another person's career" or "mistakes occur in the best of laboratories." Perhaps all of these morals apply to my story. But the reader will be in a better position to draw the proper lesson when the other tales in this book have been told.
References


