Carl Arthur Goresky

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Carl Goresky was the epitome of the physician-scientist, and even more. Two dozen scientists gathered at the Montreal General Hospital in July 1995 to give tribute to Carl's scientific contributions; they met in admiration, respect, and love for the man, rather than the symbol of science. They met to plan this book on the methods and approaches to making discoveries about cellular metabolism in the intact organ. This is part of the issue of carrying forward the information from genomics, proteomics, and molecular and cellular biology into physiological phenotyping and an understanding of the behavior of an intact organ and organism. Such research can be undertaken only by studying intact systems, an approach Carl pioneered and promoted.

Carl grew up in CastIegar, in the mountains of British Columbia, where his father was the town physician. Carl played the piano so well that he could have made a career of it; he climbed mountains, hunted, collected minerals, and worked as a stevedore on the Columbia River barges. At 16 he went to McGill, and by 22 had completed a B.Sc. and his M.D. As a part of a medical residency at Johns Hopkins Medical School he spent 2 years with Dr. Francis Chinard. Francis had pioneered the multiple indicator dilution technique for estimating solute transport and volumes of distribution (Chinard et aI., 1955). Carl brought the technology, including a sample collecting system and many ideas, back to McGill, where he completed a Ph.D. His advisor was an encouraging, brilliant man, Arnold Burgen, whose policy was to give free reign to such a "student," which was just as well because Dr. Burgen left for Oxford before the thesis was complete.

The first part of the thesis was the hallmark 1963 paper (Goresky. 1963). It demonstrated that a set of solutes passing through the liver following simultaneous bolus injection into the portal vein emerged into the hepatic vein in a characteristic way. The shapes of their outflow dilution curves were identical, relative to their mean transit time, and could be superimposed upon each other by scaling the time axis by their individual mean transit times. The observation that the curves superimposed defined all the solutes to be flow-limited in their exchange between blood and tissue: RBC, plasma protein, sucrose, sodium, and water. This conceptual step was based on the deeper idea that the capillary-tissue exchange unit was axially distributed, not a lumped compartment or mixing chamber. These two ideas, coupled with Christian Crone's demonstration that the bolus injection technique could be used to measure capillary permeability (Crone, 1963), set the stage for the use of the multiple indicator dilution technique to elucidate substrate transmembrane transport and intracellular metabolism. Carl's paper on

sulfobromophthalein published in 1964, the remainder of the thesis, did exactly that. A refinement of the analysis to correct for catheter delay was published the same year with Carl's first student Mel Silverman, who worked later with Francis Chinard.

Kenneth Zierler. Chinard's compatriot as an undergraduate and colleague as a faculty member at Hopkins, had watched Carl's development in Francis' laboratory in 1958-59, and his excellent performance as chief medical resident the next year. As a reviewer of the 1964 papers for *Circulation Research* he saw the brilliance of these: "There was so much meat in it, so creative." Of the 1963 work he said, "Carl made at least three very important points in this paper, which was obviously technically meticulous." The first point concerned the axially distributed geometry of the capillary, which Carl called a "linear two-compartment system," but which Ken preferred to call a linear two-*component* system to distinguish it from the mixing chamber idea associated with the word *compartment*. His second point was Carl's simple diagram of the system of partial. rather than ordinary, differential equations. The third was the flow-limited behavior described above.

By "technically meticulous" I think Ken was referring not only to the experimental methods but also the methods of analysis. From his first paper onward, Carl used mathematical phrasing, and characterized the biology in terms of the parameters of a precisely hypothesized physiological system. The wealth of papers that followed over 34 years had his mathematical mark upon them. Each advanced the field another step. The flow-limited transport idea applied to gasses carried by erythrocytes, the "red cell carriage effect" (Gore sky et al., 1975). The use of Michaelis-Menten expressions for saturable transformation appeared in the 1964 papers. Crone demonstrated this for transport across the brain capillary membrane barrier for glucose a year later (Crone, 1965).

The general, model-free mass balance expressions were laid out by Zierler (Meier and Zierler, 1954; Zierler, 1962a, 1962b), but Carl had developed the next stages through *model-dependent* analyses of the observations: (1) passive barrier limitation (Goresky et aI., 1970); (2) concentrative transport (Goresky et aI., 1973); (3) carrier-mediated transport (Silverman and Goresky, 1965); (4) intratissue diffusion (Goresky and Goldsmith, 1973); (5) intraorgan flow heterogeneity (Rose and Goresky, 1976); (6) transport limitations by two barriers in series (Rose et aI., 1977; Rose and Goresky, 1977); (7) reaction via intracellular enzymes (Gore sky et aI., 1983); (8) receptor binding (Cousineau et aI., 1986); and (9) oxygen transport (Rose and Goresky, 1985).

As Carl unraveled the mysteries of increasingly complex systems, he maintained the purity, even if not the simplicity, of the mathematics he used. He believed in finding the analytical solutions to the partial differential equations, and while getting advice from Glen Bach of the Department of Mechanical Engineering, fought his way through each

new method of solution. He didn't really trust the accuracy of numerical methods, I suspect, or didn't feel that they offered so much benefit that mathematical elegance could be sacrificed. I like numerical methods for the freedom of concept that they offer, and for speed of solution, but these were secondary issues for him. Carl was strongly principled.

Carl maintained close relationships with many colleagues inside and outside of McGill over his career. Foremost among these were Francis Chinard, his early mentor, and Ken Zierler, Mel Silverman, Arnold Burgen, and others. My relationship with Carl began in 1960 when Carl came to the Mayo Clinic to see his classmate Andy Engel; Carl and I were both beginning our independent studies using indicator dilution methods. Thereafter we met regularly not only at scientific meetings but also at each other's homes and institutions, sharing our efforts to sort out what we didn't understand. Carl made everyone feel a partner in these explorations; while the average guru tells one how it is, Carl helped everyone to reason their way toward an answer.

Carl's qualities as a teacher were seldom equalled. He was patient, careful, and kind, and led the residents and fellows through a topic. The GI residents loved him; when he died in the Montreal General, they all came as a group to his bedside to pay their respects. But when presenting a new topic at a scientific meeting he didn't always think of himself as a teacher but as the presenter of the information, in all its glory. Some presentations were difficult for the general aUdience, though great for the cogniscenti; Carl was modest to a fault, in the sense that he seemed to think that everyone was as smart and quick as he was. At McGill and on many occasions elsewhere he was a magnificent teacher. One of the best lectures I have ever heard, Carl gave out of the blue; he was asked to explain indicator dilution methods to an evening meeting of the National Academy of Engineering in Washington, D.C. Knowing that the biology was unknown to his audience, but that quantitative approaches were known, he gave a most erudite comprehensive review of the concepts and applications in a half hour, with just chalk and blackboard.

Carl provided leadership in the medical sciences. He edited the journal *Clinical and Investigative Medicine* throughout his last 12 years. He headed the Division of Gastroenterology at the two McGill hospitals, the Royal Victoria and the Montreal General, having brought their two gastroenterology divisions into the first merger between the two hospitals. His efforts in science and medicine were recognized for the impact he had on both. He received the Landis Award of the Microcirculatory Society, the Gold Medal of the Canadian Liver Foundation, the Distinguished Achievement Award of the American Association for the Study of Liver Diseases, and many others. In 1995 he was named officer of the Order of Canada, equivalent to a knighthood in the United Kingdom.

Behind him he leaves many colleagues who will carry on his efforts. Harry Goldsmith and Andreas Schwab, his close friends and colleagues in the research unit, Colin Rose in Cardiology, Phil Gold and Doug Kinnear in Medicine, all at the Montreal General, Eugenio Rasio and Moise Bendayan at the University of Montreal, Jocelyn Dupuis at the Montreal Heart Institute, Mel Silverman and Sandy Pang at the University of Toronto, and others scattered around the globe, continue, like myself, to learn from him and to build upon his ideas. Gone he may be, but never to be forgotten.

James B. Bassingthwaighte

References

Chinard, F. P., G. J. Vosburgh, and T. Enns. Transcapillary exchange of water and of other substances in certain organs of the dog. *Am. J. Physiol.* 183:221-234, 1955.

Crone, C. The permeability of capillaries in various organs as determined by the use of the "indicator diffusion" method. *Acta Physiol. Scand*. 58:292-305, 1963.

Crone, C. Facilitated transfer of glucose from blood into brain tissue. *J. Physiol.* 181: 103- 113,1965.

Meier, P., and K. L. Zierler. On the theory of the indicator-dilution method for measurement of blood flow and volume. *J. Appl. Physiol*. 6:731-744, 1954.

Zierler, K. L. Circulation times and the theory of indicator-dilution methods for determining blood flow and volume. In: Handbook of Physiology, Sect. 2: Circulation, Washington, D.C.: American Physiological Society, 1962, pp. 585-615.

Zierler, K. L. Theoretical basis of indicator-dilution methods for measuring flow and volume. *Circ. Res*. 10:393-407, 1962.