CURRENT ONCOLOGY

BOOK REVIEW

Book review: *Therapeutic Revolution: The History of Medical Oncology From Early Days to the Creation of the Subspecialty*

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Therapeutic Revolution: The History of Medical Oncology From Early Days to the Creation of the Subspecialty
by Pierre R. Band MD
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Dr. Pierre Band's book on *The History of Medical Oncology from Early Days* does matter—particularly nowadays, in the era of fast developments and a rising number of subspecialties with language at times too specialized to follow. From that perspective, the book's largely educational and detailed portrayal of medical oncology is hugely refreshing.

History, we are reminded by James Holland, "is written by those who win and while the vanquished may offer explanations ... such efforts rarely depict the crude reality." Band, however, does not *only* describe the history. He is part of it (together with other well-known oncology pioneers), crafting, with the Eastern Cooperative Oncology Group, the early tamoxifen and cyclophosphamide–methotrexate–fluorouracil clinical trials. His own 1961 attempts to identify programs of oncology learning constitute not only an entertaining introduction to his book, but also serve as an important reminder of how rapidly oncology has evolved, and that oncology actually emerged as a specialty only starting in the 1970s.

Why should young oncologists bother reading this book? Unquestionably, it is important to have a chronological overview of what led to the major therapeutic successes observed today, because those improvements represent hundreds of thousands of lives saved worldwide. Few realize, and Band explains, that virtually all the leukemias, choriocarcinomas, and germ-cell tumours—and most solid tumours—were diagnosed at more advanced stages and were lethal in most patients that developed them. Thus, in knowing the past, we can understand the present. Perhaps by knowing the past, we might also be able to predict the future.

In his book, Band certainly offers more than a historical aspect. With his skillful description of the events, we can follow not only the emergence of oncology legends, but also the issues of organizing oncology research—all so relevant with respect to practice today: the importance of funding and its distribution, intricacies of personalities, examples of smart observations converting coincidences into discoveries, and importantly, the need to be innovative, organized, and logistically savvy. We also re-learn the basics of medical oncology as it was explained by Skipper, Schabel, Frei, Freireich, and Holland, with the book constituting an excellent teaching tool for oncology novices.

From ancient history, we move on to Wilhelm Conrad Roentgen, Marie Claude Curie, and Antoine Henri Becquerel, the legends of the radiotherapeutic approaches dominating cancer therapy in the early 20th century. But perhaps the most relevant to medical oncology is Paul Ehrlich, the true father of modern chemotherapy, who actually coined the terms "chemotherapy," "targeted therapy," and "therapeutic index."

Extraordinary problems do require extraordinary efforts, and where there is a will, there is a way. Indeed, the U.S. Congress after World War II declared that cancer had to be conquered—or at least that efforts should start—and this is where Band's book, describing the situation of the 1950s, is at its best.

We find out that the fight against malaria is a great example. During World War II, General George C. Marshall wrote to U.S. headquarters that "while I am losing thousands of soldiers to the Japanese fire, equal if not more are lost to malaria." The reader finds that new agents for malaria were identified within a year of a task force being formed, and that one of the brightest members of the malaria team, Charles Gordon Zubrod, was, in the early 1950s, subsequently hired to organize the newly-formed U.S. National Cancer Institute (NCI). He would emerge as one of the most capable cancer strategy leaders, coordinating and execute a monumental task: create, from nothing, a well-oiled machine whose objective was to cure human cancer.

Band's description of Zubrod's systematic, meticulous organizational abilities to hire and stimulate bright young people for primary research is captivating. But before Zubrod starts at the NCI, Band reminds us that nitrogen mustard, the deadly gas of World War I, carved its true origins into oncology. That classified wartime research is picked up after World War II by Lois S. Gilman and Alfred Goodman, who noted "the marked effects of nitrogen mustards ... on lymphoid tissue.... [A]ctively proliferating cells are selectively vulnerable." What a seed for therapeutic use in the treatment of lymphoid tissue neoplasms!

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Clinical trials in Hodgkin disease follow, with Vincent T. DeVita's MOPP regimen becoming a "hallmark of cancer research," and clinical trials of nitrogen mustard "marking the dawn of modern cancer chemotherapy."

We then get to know Cornelius P. Rhoads, scientific director of Memorial Hospital in New York City in the 1940s, and his outstanding group of clinicians destined to play a major role in the development of medical oncology: David A. Karnofsky, Frederick Philips, Howard Skipper, Chester C. Stock, and later, Joseph H. Burchenal. At the newly revamped New York Cancer Research Institute, Rhoads structured a cancer chemotherapy program, establishing important links with the pharmaceutical industry, and later merging his group's activities with those of Zubrod's NCI group.

The book evolves with refreshing speed around the early NCI history, detailing all the concepts and drama of the day-to-day activities that led to curative approaches in treating cancer. We meet the meticulously organized Emil Frei and his peer, the brilliant innovator, and at times impatient but resolute Emil Freireich. Both were working with Zubrod—and with Jim Holland—on clinical innovations in leukemia.

However, no one did more for clinical oncology, Band reminds us, than Sidney Farber. A pathologist and a pediatrician, Farber often left his microscope to attend to children dying of leukemia. Farber's success starts with the identification by Lucy Wills of the essential "Will's factor" that helped with the recovery of "anemia of pregnancy" and that was subsequently purified by the brilliant Yellapragada Subbarow (from the U.S. branch of Lederle) as folic acid. If folic acid is an essential ingredient in cells, why not block it as part of cancer therapy?

The ingenuity of Subbarow in a short while produced a chain of anti-folates that were passed on to Sidney Farber. In no time, aminopterin was given to gravely sick children. The foundational 1948 *New England Journal of Medicine* paper by Farber was the first reported chemotherapy success in leukemia. That work stimulated still others: James Holland in New York, Zubrod's group at the NCI, and Burchenal and Karnofsky from Rhoads's group at Sloan Memorial in New York City.

Band then marches on with more drama of coincidental observations: Min Chiu Li observed reduced levels of human chorionic gonadotropin (HCG) after treatment with methotrexate in his melanoma patient. Why not apply methotrexate to malignancies that produce high levels of HCG? And so began treatment of choriocarcinoma, until then a lethal tumour with almost 100% mortality. All of the first three patients responded, and eventually many were cured with prolonged methotrexate inductions until HCG levels dropped to zero. The concept of "treatment in remission" as a condition for cure was thus born. Band reminds us that those principles, rapidly modelled by Skipper in Alabama, and by the NCI's Holland, Frei, and Freireich, paved the way for cures in leukemia. Observations concerning the treatment of microscopic cells became extremely relevant for today's oncology. As seen with new-generation chemotherapy and with biologic treatments, the concepts elucidated then are still valid in therapy for most human malignancies, and will likely play pivotal roles in cancer prevention.

Other examples of alert observations in this book are worth noticing: a wire falling into a dish of *Escherichia coli* helps to identify the activity of platinum against multiple tumour cell lines. The rest is history, with Lawrence Einhorn in Indiana, and others in New York, eventually revolutionizing the treatment of germ cell and testicular tumours—malignancies that were more than 90% lethal until the discovery of cisplatin. Lance Armstrong's dramatic recovery from a metastasizing testicular tumour attests that "surviving" is not only a reality after treatment with toxic agents, but that supramaximal cardiovascular efforts are also possible in survivors, despite an otherwise lethal malignancy and close-to-lethal therapy.

Band flashes through the subsequent milestones of solid tumour developments: combination chemotherapy, first-order kinetics, dose scheduling, and the formation of collaborative trials—all of which pave the way to significant mortality reduction for multiple cancer sites. The cancer modelling of Goldie–Coldman and Simon–Norton would clarify the black hole of resistance and also lead to neoadjuvant chemotherapy, dose escalation, and dose density in chemotherapy.

An excellent description of the estrogen receptor discovery follows, a true "revolution" in "targeted therapy" of cancer, enabling new approaches for breast cancer as conceptualized and executed by Elwood V. Jensen. The reader will also sense success with Nicholas Bruchovsky's identification of dihydrotestosterone and the nuclear androgen receptors in prostate cancer. All had to be blocked, but Bruchovsky's eventual proposal for much less toxicity and higher quality of life with intermittent rather than continuous androgen suppression was a big innovation.

Also, one cannot skip Norman Jaffe's struggle with randomization to implement a curative therapy for osteosarcoma. That is where the statisticians and clinical trials dominating today's arena of clinical research stepped in: indeed, if differences are large, no "controls" might be possible; but for detecting small differences, large randomized controlled trials are essential. Band provides, in Jaffe's case, a flavour of what was likely to emerge in the decades come.

Nothing compares to the lion's share of brilliancy from Bernard Fisher, initially with perioperative chemotherapy, and later, in the 1960s, with the formation of the colossally successful National Surgical Adjuvant Breast and Bowel Project—a cohesive multi-institutional group (more than 160 centres by 1980s) coordinating surgeons, medical oncologists, and statisticians and staging clinical trials with a speed and efficiency never before seen in history. The defeat of the Halsted radical mastectomy dogma and the emergence of conservative lumpectomy and adjuvant chemotherapy outmatch in their importance many oncology developments, because they affect hundreds of thousands of women worldwide.

Ultimately, it would be the power of cooperative trials, with large patient samples, that would increase the speed of clinical trials and foster the formation of the Cancer and Leukemia Group B, with its trials 1, 2, and 3, and later, the Eastern Cooperative Oncology Group, with Band's own contributions to melphalan, cyclophosphamide–methotrexate–fluorouracil, and tamoxifen. Ultimately, Louis

Trench, Craig Jordan, and collaborative groups propelled tamoxifen into fruition through the long chain of international breast cancer trials.

The reader is motivated because nothing is apparently beyond reach. Researchers who already investigate cancer can investigate it more effectively. Those considering working in the cancer arena will be stimulated more. The junior co-author of this review, a Public Health graduate, read the book thoroughly and is now firmly interested in medical oncology. Most of the book's future oncology readers will likely ask not only what medical oncology history means to them, but also what their team efforts could mean for oncology's future. All those reactions signal the great value of Pierre Band's book. Highly recommended.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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