BOOKS: PHARMACOLOGY

Developments from a Beneficial Bark

William P. McGuire

The journey of a new drug to the shelf of your local pharmacy is always a hazardous voyage. In the United States, the process begins with drug discovery and then proceeds through formulation, animal toxicology, and pharmacology; human toxicology (phase I trials); human efficacy evaluation (phase II trials); and relative efficacy evaluation (phase III trials). At some point along this path (typically after either the phase II or III evaluation), a New Drug Application is submitted to the Food and Drug Administration (FDA). If favorably reviewed, the drug becomes commercially available. Drug development requires large amounts of capital, and there is a significant chance of failure at many points along the way. The process may be halted because of problems with formulation, lack of efficacy, unacceptable toxicity, or failure to improve on the therapeutic indices of similar, already available drugs in the same class.

The Story of Taxol Nature and Politics in the Pursuit of an Anti-cancer Drug
by Jordan Goodman and Vivien Walsh
Cambridge University Press, New York, 2001. 296 pp. $27.95, £18.95. ISBN 0-521-56123-X

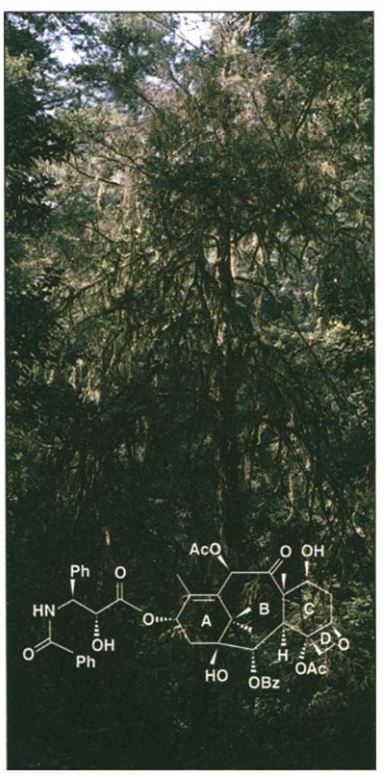
For anti-tumor drugs, the screening of new agents and much of their preclinical and clinical evaluation has often been sponsored by the National Cancer Institute (NCI) through extramural grants and contracts. When the bulk of development is complete, the pharmaceutical industry bids on rights to market the drug. The course and consequences of these interactions between publicly funded research and corporate interests are often controversial. In *The Story of Taxol*, Jordan Goodman and Vivien Walsh, historians at the University of Manchester Institute of Science and Technology, details one such case, the development of the anti-cancer drug paclitaxel (the generic name approved at the time Taxol was trademarked).

The crude extract that would become paclitaxel was initially identified by the NCI's screening program in 1966 and found to have broad anti-tumor activity. But FDA approval for the use of the drug in ovarian cancer did not come until 1992. Development took significantly longer than the five to ten years that typically elapse between drug discovery and approval for human use. The process was slowed by formulation problems. In addition, the collision of a host of political forces further impeded the rapid deployment of paclitaxel even after it became clear it was a broadly active agent. These forces included the NCI, the Department of Agriculture (USDA), the Department of the Interior, several environmental groups, and a swarm of some unusual characters from the Pacific Northwest who were hired to collect bark from the Pacific yew (*Taxus brevifolia*), the original source of paclitaxel.

The NCI screening program had been successful in the development of synthetic anti-tumor drugs, but the only natural products on the market in the 1970s were the vinca alkaloids. These were originally intended to be hypoglycemic agents. Although the NCI played a major role in the clinical development of the vincas, they were not from the NCI–USDA screening program. When Monroe Wall first identified anti-tumor activity in a crude extract of *Taxus brevifolia*, the NCI had to depend upon the USDA to collect bark, the richest source of the active compound. Unfortunately, some strained relationships between these two agencies led to multiple delays in bark acquisition. Further, staff in the Investigational Drug Branch of the NCI, who were responsible for the clinical evaluations, underestimated the activity of and interest in the compound. Thus, supply was always lacking as demand increased. Even before the FDA approved paclitaxel for recurrent ovarian cancer, the drug's activity in both lung and breast cancers was apparent. Because there are 35 times more lung and breast cancers than ovarian cancers, it was no surprise that supply of paclitaxel became a critical issue.

In response to the public outcry for paclitaxel, several private bark collectors became involved in the process to help the NCI make adequate supplies available. Pacific yew, however, is a tree primarily found in the Northwest's old-growth forests, home to the spotted owl. Environmental groups opposed to destruction of this natural ecosystem thus had another, more human icon as their champion, the patient with ovarian cancer unable to get paclitaxel because of poor conservation practices. The news media was soon replete with stories of dying cancer patients unable to obtain this "lifesaving" drug due to ineptitude at the NCI, an avaricious logging industry, dishonest bark collectors, and the like.

To increase production and make supplies of paclitaxel available quickly, the NCI turned to capital investment from the private sector. In late 1989, it selected the pharmaceutical company Bristol-Myers Squibb as its partner in a Cooperative Research and Development Agreement for taxol. Bristol-Myers Squibb accomplished the goal for which it was "hired." Bark procurement and paclitaxel production were scaled up, and news stories about lack of drug vanished. Very quickly, Bristol-Myers Squibb recognized the importance of having a supply source that was not dependent on bark and sought to develop alternatives. Eventually, a semi-synthesis from a precursor found in the yew's needles (a renewable supply) was patented, and harvesting trees for paclitaxel is no longer an environmental threat.



Freed from yew. The completion of two total syntheses in 1994 allowed taxol to be produced from inexpensive starting materials and removed the need to harvest raw materials from the trees.

Goodman and Walsh end their book at this point. Their detailed, well-researched account will be enjoyed by historians and scientists interested in the drug-development process and its many potential pitfalls.

In Hollywood, successful movies are often followed by sequels. I await *Story of Taxol II*, which could deal with the legal battles that have surrounded paclitaxel since the end of the period covered by Goodman and Walsh. When Bristol-Myers Squibb's exclusive rights to paclitaxel expired, it came to light that the company had patented the method of administration and had used this patent to block the entry of several generic and less expensive alternatives. Bristol-Myers Squibb fought

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and lost the ensuing legal engagement (I appeared as an expert witness for their opponents), and paclitaxel will soon be available at a significantly cheaper price. Additional cases surrounding who owns the patent rights to the semi-synthetic process are still on the court docket.

In any event, *The Story of Taxol* presents an informative account of a complex history. Taxol remains the single most prescribed anti-tumor agent and has generated billions of dollars for Bristol-Myers Squibb. I agree with the authors' conclusions that the development of taxol was marked by bureaucratic ineptitude, private industry avarice, and a modicum of benefit for many cancer patients. The economic success of paclitaxel has led many pharmaceutical companies to enter the drug-discovery arena at a time when the NCI has begun to exit. It is my firm hope that their participation will improve the quality, quantity, and developmental speed of drugs made available to the patient with cancer. Whether this approach is financially feasible for the patient remains to be seen.

BOOKS: CONSERVATION

Ingredients for Tropical Renewal

Valerie Kapos

In these days of increasing pressure on researchers to justify what they do in practical terms, most ecologists and field biologists would cite the importance of their work for conservation. However, too few such scientists recognize that biology is just one small piece of the conservation puzzle, which is made up mostly of political, social, and economic elements. *Green Phoenix*, a narrative account of the evolution of Costa Rica's small, under-resourced Santa Rosa National Park into the impressively expanded and managed Guanacaste Conservation Area, brings this reality home. Science writer William Allen spotlights a key example of where researchers have become involved in these other aspects of conservation with great effectiveness.

Green Phoenix
Restoring the Tropical Forests of Guanacaste, Costa Rica
by William Allen
Oxford University Press, New York, 2001. 332 pp. $35, £22.95. ISBN 0-19-510893-0.

The book is a difficult one to describe or place in one's mental library catalog. It certainly does not fit in a science section, nor even in popular science. Although it could be shelved under conservation or environmental activism, parts of it might qualify as biography, some is about politics and economics, and other parts fall under natural history. This classification difficulty, which stems from both the complex nature of the subject and the rather discursive way in which the book is written and organized, makes it difficult to define the author's target audience.

As a scientist and field biologist, I found much of the science and natural history rather irritating in their wide-eyed superficiality. Nonetheless, I found the lessons about the principal needs and activities for establishing a functioning practical conservation and restoration program very useful. For many of us in the conservation sector, these lessons have already been learned, at least in theory, but the specific examples are valuable, as is the concise synthesis of the lessons in the much better structured epilogue.

Allen provides readers a regional background covering basic research and the environmental pressures that together demonstrated the need to expand the original reserve and to restore forest cover. The issues and challenges covered include: the necessity of controlling fires, while still somehow limiting the standing biomass of exotic grass; problems caused by the limitation of dispersal of tree seeds through lack of appropriate fauna; and principles of landscape ecology and the need to connect habitat fragments. The author also discusses some of the solutions scientists and volunteers employed in the field.

For me, the real value of the book kicks in where science and its application ends and Allen addresses the vital roles of politics, sociology, economics, and (incidentally) personalities in achieving conservation goals. The influences of politics—from local (harnessing the influence of powerful landowners and vested interests) to national and international (U.S. involvement and interests in Nicaragua)—emerge clearly, if in rather fragmented form. The author emphasizes both the importance of education in generating local support for the conservation area and, interestingly, the importance of basic research in adding to the perceived value of the site. His detailed accounts of the acquisition of additional blocks of land for the park and of the fund-raising and politics involved illustrate very effectively the magnitude of effort and the kinds of focus required for such work. Guanacaste's most interesting economic lesson is the importance of generating an endowment to provide both sustainability and room for making short-term errors in the management of a conservation project.

Returning trees. Beyond Dan Janzen, the Guanacaste lowlands stretch from Santa Rosa National Park to the slopes of Volcán Orosí and Volcán Cacao.

CREDIT: WILLIAM ALLEN

The influence of personalities and the importance of leadership are highlighted through the book's focus on the key role Dan Janzen played in the development of the Guanacaste Conservation Area. While noting that Janzen doesn't want to be lionized, the author proceeds to do just that. In doing so, he appears to place less weight on the roles of other individuals and, especially, on the course of events from a Costa Rican perspective. I can't help wondering what Janzen himself thinks of the book.

In his conclusion, Allen recognizes that some of the lessons from the Guanacaste project depend on its unique local situation, but he ventures little comment on their applicability in other contexts. This is one of several respects in which I found myself frustrated and wanting to know more. Another is the extent of information Allen provides about the restoration program and its impact. Maps and illustrations of the progress of the reforestation would have helped a great deal in this respect and would have been a very useful addition to the book's photographs of personalities and landscapes. Despite these frustrations, I found *Green Phoenix* informative and inspiring. It offers a fresh perspective on scientists' involvement in practical conservation.

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