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REVIEW OF REVIEWS

E. Leong Way

Department of Neuropsychopharmacology (Tsumura), Gunma University School of Medicine, Maebashi, Gunma 371 Japan and Departments of Pharmacology and Pharmaceutical Chemistry, University of California, San Francisco, California 94143

This is to be my last contribution in this series to this volume. Bob George and Ron Okun are finishing their stint as editors and the fact that they were both students in the Pharmacology Department at the University of California at San Francisco when I was on the faculty tells me that I should also step down. I have been writing Review of Reviews, which I inherited from my predecessor and teacher, Chauncy Leake, since 1979. Bob and Ron were stimulating and so much fun to work with. The new editors will bring a fresh outlook but with the valuable experience they gained under Bob's and Ron's tutelage.

THE PHARMACEUTICAL INDUSTRIES

Drug manufacturers in the United States have played a highly important role in improving the health and economic status not only of Americans but of people throughout the world. Books have been written about these contributions, while others have criticized their greed and materialism. Within the past year three volumes have appeared which give a more total picture. The authors of each book describe various facets of the role, impact, growth, and development of the pharmaceutical industry. Along with these changes, there were restraints voluntarily and involuntarily imposed on them that contributed to a maturing of corporate responsibility. The advancements were abetted in part by wars and regulatory actions.

Wars are devastating, but sometimes some good results serendipitously. Certainly, war stimulated the growth of the pharmaceutical companies because the disruption of supplies forced existing facilities to expand and new ones to be created.

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Regulatory processes also promoted the size and quality, if not the number, of companies. Regulation has its advantages and disadvantages. To safeguard the health of the public at large, fair regulation is mandatory but overzealous regulation can result in loss of benefit. Governmental regulations imposed on the pharmaceutical industry favored the strong over the weak because small companies generally did not have the resources to meet regulatory requirements. However, those companies that survived generally became stronger, with increased capabilities for serving the public.

Swann (1) authors a fascinating account of the interactions between academic scientists and the pharmaceutical industry. The interest is engendered by his willingness to dig thoroughly into the literature and the intimate insight he is able to provide from gleaning the personal papers of some of the more successful individuals. Familiarity with the names of well-known professors heightens the interest for the reader. These academicians not only made an impact on health-care by their scientific contributions but also influenced corporate policy through their perspicacity and force of personality. Pharmacologists given starring roles are Alfred N. Richards with Merck, Arthur Loevenhart and Arthur Tatum with Parke-Davis. Featured less but mentioned often are well-known giants of the recent past; John Jacob Abel, K. K. Chen, Chauncy Leake, Harry Van Dyke, and Hans Molitor. Luminaries from other scientific disciplines include, to name but a few, Roger Adams, F. G. Banting, C. H. Best, G. H. A. Clowes, George Whipple, and George Minot.

The interactions between some of these academic consultants with pharmaceutical companies resulted in substantial benefits not only to the corporations but also to the individuals and their educational institutions. The agreements between the parties differed considerably and consequently the rewards were not always commensurate or fair.

Perhaps the two most successful academic consultants were Alfred Richards and Roger Adams. Richards from the University of Pennsylvania, renowned for his studies on the renal glomerulus, had close ties with Merck, while Adams, a chemist at the University of Illinois with talents for organic synthesis, maintained a liaison with Abbott. Both men began as scientific consultants but, by virtue of their scientific acumen and wisdom, eventually became involved in decision-making processes and in formulating policies. Both became integral parts of the corporate structure and were elected to the Board of Directors while maintaining their university ties. They served their respective companies throughout their professional careers and as a result both men and their academic institutions benefitted handsomely from the relationship.

Relations between academe and industry were not always without friction. Both parties were interested in getting therapeutic agents for the benefit of the public as soon as possible. However, not altogether surprisingly, the uni-

versities had strong feelings against monopolies and commercial exploitation, whereas the companies wanted to recoup their investments as early as possible ahead of the competition. Despite these conflicts, compromises inevitably secured huge benefits for all parties concerned, including the public.

The University of Toronto and Eli Lilly Co. began their negotiations amicably enough. However, soon after the contractual agreements were signed their differing philosophies led to some arguments; a hidden agenda was concerned with the distribution of insulin and the selection of personnel for its evaluation. Assigning patent rights to the University for the isoelectric method of producing insulin and allowing Lilly the use of Iletin as a brand name for insulin resolved the hard feelings. In the end, insulin became highly profitable for the company and greatly enhanced their stature, while the laboratories of three of the codiscovers of insulins, F. G. Banting, C. H. Best, and J. B. Collip, were largely subsidized by the royalties.

Harvard and Rochester also had agreements with Lilly but their relationship was smoother than that experienced by Toronto. Much of the dealings between Lilly and the two American institutions were based on a gentleman's agreement.

George Minot and William Murphy, who made the discovery while at Harvard that fresh liver could maintain patients with pernicious anemia, decided in 1927 to join with Lilly to develop a suitable extract in preference to several other companies with similar desires for collaboration. In the first place, Lilly had a similar project ongoing and, secondly, the company had attained considerable repute in developing commercial insulin with Toronto. No written contractural agreements were made between Lilly and Harvard, but the company agreed to provide appropriate amounts of a liver extract which was to be processed as outlined by E. J. Cohn, a physical chemist at Harvard who had been called upon earlier by his two clinical colleagues to isolate the liver principle. In turn, Minot and Murphy would test the liver extracts provided by Lilly. In the beginning, Lilly did not follow this arrangement strictly and delayed in providing the liver extract for testing because their chemists were attempting to develop their own extract, which would be patentable. However, when the Harvard Committee on Pernicious Anemia, which had been appointed to oversee the program, exerted pressure, Lilly acceded to their wishes and accelerated their efforts to furnish more liver extracts. In general, therefore, the relationship between Lilly and Harvard was quite good. Indeed, after Lilly patented their liver extract no-343, the company gave the patent to Harvard who then turned it over to the public.

Likewise, the agreements made between George Whipple at Rochester with Lilly during the developmental stages of a liver extract for secondary anemia were verbal. Earlier, Whipple's animal data on liver extracts had paved the

way for the studies of Minot and Murphy. Whipple began his experiments at the University of California at San Francisco and continued his studies after moving to Rochester. Familiar with Lilly's roles with Toronto and Harvard, he readily accepted an invitation from Lilly for a collaborative effort to develop a liver extract for secondary anemia. As a result of this joint successful effort, Lilly placed liver extract no. 55 on the market after obtaining prior permission from Whipple to patent the product. Although Whipple appears to have played an important role in developing the extract, personal ethics would not allow him to have his name on a patent, but from prior experience, he was quite willing to place his faith and trust in industry. While Whipple was at the University of California, he had been involved with the canning industry during a botulinus outbreak. His colleague at the Hooper Foundation, Karl F. Meyers, had more or less saved the industry by developing a canning method to prevent botulism. Whipple was impressed by the industry's conduct during this crisis and hence had no qualms about collaborating with Lilly. His agreements with Lilly during the developmental phases on the liver extract were negotiated as the work progressed, but just before marketing Liver Extract no. 55, a contractual arrangement was signed between Rochester University and Lilly, presumably at the insistence of University administrators. The profits enjoyed by Lilly allowed the company to endow Rochester with funds to support Whipple's research until he retired in 1955, establish a chair in pathology, a scholarship program for premedical and medical students, and a visiting lectureship fund to be used at the discretion of the Board of Trustees.

The book is rich in detail, but I could supplement with a few items of interest. One concerns my imaginative teacher and endearing life-long friend, Chauncy Leake. Although Chauncy's name was brought up several times, no mention was made of his rewards. In fact, what he reaped for himself and the University of California was not very much. His laboratory played a major role in the development of divinyl ether as an anesthetic, nalorphine as an opiate antagonist, carbarsone as an intestinal amebacide, and amphetamine as a central nervous system stimulant, but neither Leake nor his department received significant financial benefit from these discoveries. His altruism did not permit him to apply for patent rights, although his more astute and practical associate, Gordon Alles, made a small fortune from a use patent for amphetamine and the agreement he negotiated with Smith Kline and French.

Secondly, although the author pays much tribute to the pharmaceutical industry's munificent support to academe, he neglects to even mention its most important arm. In this instance, the companies acted in concert rather than separately and received no direct economic benefits for their innovative project. The Pharmaceutical Manufacturers Association, recognizing the need to develop young scholars with research talent, established the PMA Founda-

tion in 1965. Since its inception, PMAF has focused on fields of research related to the biological and pharmaceutical sciences where there is growing need for teachers in pharmacology, toxicology, and pharmaceutics. In 1966, the PMA Foundation's grant program began modestly awarding a few grants amounting to $101,000, but by 1989, fifty-eight young scientists were named recipients of a record $2,103,564 in grants. In their twenty-four years of existence, over 700 scientists have been assisted through the Foundation's grants program and many awardees have become established research scientists, teachers, departmental chairpersons, and responsible senior administrators in industry and government (2).

In final summation, the book is recommended highly because it is informative, interesting, readable, and affordable. It should enjoy a long shelf-life.

In another book, Libenau (3) provides a history of the pharmaceutical industry in the United States and analyzes the causes of its growth. The years between 1890 and 1930, in his view, were decisive and he describes the events that were critical. His account traces the birth and growth of the better-known pharmaceutical concerns located near Philadelphia that are in existence today.

The foundation for the pharmaceutical industry was laid shortly after the War of 1812. Previously, the newly liberated colonists were still dependent on Britain for most of their medicines, but disruption of these supplies necessitated their manufacture in the United States. Apothecaries took over and their laboratories were turned into manufacturing plants for larger-scale production. The Civil War promoted further rapid expansion of some of the more successful firms.

The growth of these concerns evolved as the need for standardization and better technology developed. However, there were ups and downs because some overly materialistic companies created problems. Despite these peaks and valleys, both conditions seemed to help the growth of the ethical companies. Their policy of not advertising their prescription products for sale to the general public did not necessarily prevent them from staking claims on their own over-the-counter remedies. The successful companies of this era survived in large part because they coordinated their efforts in science, medicine, and business.

The major therapeutic agent that established the modern pharmaceutical firm was diptheria antitoxin. Large-scale production required standardization and improvement in production procedures, which, in turn, necessitated the establishment of control and research laboratories within the organization. The companies became highly competitive in the quality of their products. The wide variations in quality resulted in enactment of regulatory legislation which allowed the larger scientifically based companies to grow even bigger.

The growth of some of these firms located mainly in or near Philadelphia are described. Companies receiving most attention include R. K. Mulford, H. M. Alexander, Smith Kline and French, Wyeth and Lederle.

One of the more successful companies marketing diptheria antitoxin was the Mulford Co; it later merged with Sharp and Dohme, which, in turn, was acquired by Merck. Mulford began in 1891 as a small manufacturing pharmacy but grew rapidly as it earned a reputation for high-quality, well-advertised products. The company's rapid success was due largely to the close relationship it fostered with pharmacologists in universities and with leading physicians in hospitals. Torvald Sollman, an eminent pharmacologist, helped Mulford gain an early foothold in the diptheria antitoxin market by developing a potent, stable product that was less painful when injected. Subsequently, however, Mulford became embroiled in a dispute with other companies over their smallpox vaccine, particularly H. M. Alexander and Parke Davis. In 1901, an outbreak of tetanus occurred in Canada after inoculation of a smallpox vaccine produced by Mulford. Alexander attempted to exploit this situation and there were bitter exchanges between these two competitors. The squabble did not enhance the reputation of any of the companies producing smallpox vaccine. The consequences were resistance by the public toward its use and an outcry for regulation of its manufacture.

Congress passed an act in 1902 to control the production and sale of biologicals, including antitoxins, vaccines, serums, and analogous products. Thus, for the first time, manufacturers had to face regulations that required licensing and inspection. The responsibility for constant monitoring was assigned to the US Hygienic Laboratory and the once cooperative relationship between government and industry became, in part, adversarial. This legislation paved the way for the enactment of the Food and Drug Act in 1906, which was intended primarily to control adulteration in food and, to a lesser extent, patent remedies. The main target among the latter group were nostrums containing unduly high amounts of alcohol and narcotics. As a consequence, companies with the means and established scientific base to meet governmental requirements grew even more. This expansion was also accompanied by increasing growth of the FDA to cope with the ever-increasing demands of consumers and legislators for stricter regulation of the pharmaceutical companies.

The story that is told is fine as far as it goes but it doesn't go far enough. I would have preferred more complete coverage in time and place. Here we are about to enter the twenty-first century, but the chapter is closed in 1930 instead of 1980. And yet, the last fifty years have been a golden period of drug development and company growth. Probably over ninety percent of the drugs being prescribed today have been introduced since World War II. These matters were touched upon so lightly in the final paragraph of the book that the reader is left hanging in mid-air. Also, some threads were difficult to

follow, although the development of a few companies were described in some detail. However, I lost track of the fate of the H. M. Alexander Company which was so influential at the beginning of the century and gave Mulford so much competition. Still, the book makes interesting reading and leaves one anticipating the appearance of chapter 2 of a serial.

In yet another book, Spilker (4) authors a comprehensive compendium on the development and marketing of drugs and includes a highly knowledgeable analysis of the more important issues involved. He makes no claims of originality and indeed, borrows freely from the excellent bibliography he provides. However, the book is different because Spilker skillfully blends his reference sources with his own philosophy and experiences to produce a volume that could well turn out to be a bible for the trade.

Junior and senior executives in the pharmaceutical companies are the main audience targeted, but even scientists inside and outside the industrial hierarchy would benefit from reading the book. In fact, some of the contents would make a first-rate text for the scientific edification of students from the junior high school up through the university graduate level.

The book is divided into five main sections: I: Drug Discovery, II: Corporate Organization and Management, III: Research and Development Organization and Management Issues, IV: Technical and Functional Issues and V: External Interactions and Relationships. Most of the scientific facets are discussed in Section I, but Sections III and IV also include much practical science as they cover the judgment process for deciding the number of drugs to develop simultaneously, for evaluating a portfolio of new drugs and for designing studies in toxicology issues and clinical drug development. However, chapters 2 and 3 of Section I, covering the nature of drug discovery and development and how scientists and clinicians evaluate and interpret data, provide one of the best lay expositions of how the scientific approach is applied to gain understanding and meaning. And in explaining the scientific basis for decision-making, he gives cogent reasons why, despite the spectacular advances in molecular biology and technology, further progress cannot be made without some old-fashioned empiricism and why this type of application cannot be replaced. Molecular pharmacology may provide short-cuts in the approach but the detailed information necessary before marketing requires classical methodology that is not always routine and that may require improvisions.

What I have just described is only part of the big picture Spilker covers on the issues in drug-discovery development. The jaded reader may opine that the book is no more than a handbook of how to develop a successful drug. However, it would be grossly unfair to compare this volume with those telling how to win on the gaming table or invest in penny stocks. Spilker's book is a serious, comprehensive endeavor to treat the issues. In addition to the highly useful bibliography, some interesting data are revealed, such as the leading

companies' best-selling drugs and the number of drugs constituting 50% of a companies sales. His golden rules for success are a mixture of ethics, pragmatism, clichés, common sense, experience, and wisdom. At times, some of the suggestions may appear obvious and sound a bit patronizing, but the ingredients are masterfully combined into a successful recipe.

KAMPO MEDICINE

Hosoya & Yamamura (5) edited a volume on Kampo (Japanese herbal) medicine which has its roots in traditional Chinese medicine. Diagnosis and treatment in Kampo medicine is alluded to as Sho and Ko, but these two terms are not altogether synonymous with their Western counterparts. Sho circumscribes a profile of signs and symptoms without naming any actual disease, but once the syndrome is identified, treatment is initiated with a corresponding Ko. Ko consists of a decoction of fixed composition formulated from several natural products that is given after the Sho is determined. Since Sho may vary from day to day, so then also must Ko.

The absence of a stable steady-state for making assessments subjects Kampo medicine to criticism despite the fact that its empiricism, in certain instances, may have withstood the test of time. To the proponents of the Western school who seek to isolate the active constituent of a natural product and evaluate it on a specific disease, there is much skepticism about the merits of Kampo medicine. However, it is entirely conceivable, indeed to be expected, that the efficacy and toxicity of a drug can be altered by products with which it is combined. Hence, investigators in Kampo medicine have attempted to provide a rational pharmacologic basis for the claims of enhanced potency and lowered tendency for adverse effect of Kampo medicines. For example, by testing for antitussive activity in a herbal decoction for treating asthma, Hosoya showed that the active plant was *Ephedrae Herba*. Although a decoction of this herb was the most potent pharmacologically, the complete prescription containing four products was much longer-lasting. He also provided experimental data indicating that the anticonvulsant effects of a nine-herb decoction (TJ-960) could be assigned to one or two plants but potency was reduced when the other products were omitted from the recipe. More than fifty articles are contained in this volume and the vast majority report laboratory or clinical data of herbal prescriptions on the endocrine, circulatory, immune and central nervous systems, as well as on treatment of allergies, hepatitis and nephritis.

Although drugs used in humans have been evaluated empirically for centuries, modern clinical pharmacology with double-blind assessments emerged as a discipline only in the 1950s. However, the rigors of the discipline tend to limit the sensitivity of the methodology—as illustrated by the lack of a ra-

tional explanation for acupuncture until the discovery of endorphins. Despite some variation in the quality of the presentations, in general the investigators display genuine interest in seeking scientific answers in a very difficult area. I found the volume to be interesting and informative.

REGULATORY PAIN

Hill & Fields (6) have edited a volume expressly to lobby in behalf of patients suffering from pain, especially cancer. Their prime targets are practicing professionals and the intent is not only to educate about treatment of pain but also to seek support to mitigate attitudes and laws regulating analgetic medication. The chapters represent the written articulations of experts selected to speak at a conference concerned with the various aspects of pain treatment in a drug-oriented society. The underlying message is that many physicians and nurses have "opiophobia." They tend to underutilize analgetic medication partly because of insufficient pharmacologic knowledge and exaggerated fears of producing addicts, but primarily because of the consequences of governmental regulations encroaching on medical practice. The barriers range from intimidation, harassment, to just being bothersome. However, what is a nuisance to the practitioner can be a very serious matter to the patient who is in severe pain and for whom a mild analgetic is prescribed because more effective opioids require prescription in triplicate and record-keeping.

To the enforcement official, the legislation is not designed to interfere with medical practice and therefore should not cause problems for physicians prescribing opiates legitimately. However, it was pointed out that no matter how well-meaning the intent, the legislation just pays lip service to noninterference because the mission of enforcement is to prevent diversion rather than to support the practice of medicine. Consequently, when the zeal of enforcement is directed against a few violators problems are created for the vast majority of physicians, to the patient's detriment. Scheduling of drugs is cited as an example. Relatively little evidence is required to reschedule a drug from Schedule III to II, but it is almost impossible to justify the reverse. Methylphenidate has been a Schedule II drug for nearly two decades, despite evidence for its usefulness in treating narcolepsy and attention-deficit disorder and little evidence for its abuse.

Physicians and nurses are advised that the highest priority should be accorded to maximizing pain control and the patient should be given as much opioids as needed. The fear of producing addiction should not be a major consideration. The patient is the best judge of how much pain is present and some physicians have observed that when patients are allowed to control opiate medication on their own, effective pain relief is achieved without addiction. These points were stressed to improve attitudes and legislation on opioid usage.

The necessity for enlightened professional responsible for prescribing and regulating opioid with the addiction potential is made even more acute by the current media hype given to the "War on Drugs." Remedial measures should include re-education as well as continuing education about pain and the pharmacology of analgetic agents, giving more responsible roles to pharmacists, as well as maintaining and improving communications with legislators and enforcement officials. Although individual contacts are useful, the efforts would be more effective if concerted action is coordinated and mediated through professional societies.

POPULAR SCIENCE

Goldberg (7) writes about the discovery of brain peptides with opiate-like activity (opiopeptins, endorphins, enkephalins, dynorphins). The title of the book is a bit misleading because it connotes a thorough dissection of the background and events that led to the achievement. Although not a scholarly historical treatise, it is very good story-telling for popular consumption. The writer has succeeded because of his skill in dramatizing the personalities and the events involved in what was a very exciting race.

Most of the investigators engaged in the contest happen to have very strong personalities and were intensely competitive. Their egos and biases were exposed by the artful manipulations of the writer who felt little constraint in expressing the notions he had formulated after interviewing the main personalities, those close to them and others not so close. Most of the contestants were also established scientists, the main exception being the eventual winner, John Hughes, with his better-known coach, Hans Kosterlitz, who were abetted in the closing stages on the chemistry by Linda Fothergill, Barry Morgan, Howard Morris, and Terry Smith.

It is only poetic justice that the Aberdeen group won. The initial stage was set through the stubborn efforts of one young, irascible investigator in the classic setting with a benevolently tyrannical, "retired" teacher. They were pitted against some high-powered research teams in the United States whose laboratories were richly endowed with government funds.

Some of the runner-ups deserved a better fate. C. H. Li and Avram Goldstein came so very close. With a little better communication and coordination they might well have been the winners. My personal bias would have made me very unhappy had some other Johnny-come-lately laboratory succeeded in isolating the first opiopeptin. Li probably was the first to isolate a pure opiopeptin, but β-endorphin sat on the shelf ignored because he did not know what to do with it. Goldstein knew what to do with POP_1, but he did not know until it was too late that it was β-endorphin and that Li had it.

Left in the wake were the also-rans, but their thoughts and work as well as

those of other noncontestants helped to pave the way. In fairness, the originality of the more recent, successful investigators was not in the conceptualization of the approach, but rather in the ability to use the right tools to solve the problem. Since widely-read books often become gospel a few names should be inserted for the record.

The most serious credit-omission by the author as well as by the investigators he wrote about is that concerning naloxone, which everybody seems to take for granted. Naloxone was the essential tool used to guide the way. Its codiscoverers were Harold Blumberg and Jack Fishman, whose inspiration was derived from earlier work on nalorphine by Elton McCawley, Ross Hart, and Chauncy Leake. Also, many had thought of the possibility as early as, if not before, Kosterlitz, that morphine mediated its effect on receptors that might have native ligands. G. Ungar and F. Huidobro had the right idea—but not the solution. They tried to isolate the substances morphine was mimicking but failed to design the proper experiments. The stereospecific approach to identify opiate receptors was applied in the fifties and sixties before Goldstein, Pert, Snyder, Simon, and Terenius used similar concepts and succeeded. The extraordinary effects attributed to the opiopeptins are no different from what has been known for years about opiates. The cataleptic effects of β-endorphin was media hype generated by scientists who were ignorant of or chose to ignore the facts. The opiopeptin effects noted on the pituitary hormone function merely followed the wake of data obtained by R. George and N. Kokka on morphine nearly two decades earlier.

The discovery of the opiopeptins has had a tremendous influence in biomedical science. The impact is truly worthy of an Nobel award but the politics of proper credit has delayed the recognition. Goldberg tells about the maneuverings and the politics that may occur in the selection process. If, as they say, the Nobel Committee likes to name three recipients (now that Li is deceased), I say Hughes, Kosterlitz, and Goldstein. The book makes easy reading and the science is understandable to the lay person. It is available as a paper-back or hard-cover and well worth the price.

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