STEROID DRUGS

NORMAN APPLEZWEIG
Director, Norman Applezweig Associates
Consulting Biochemists

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PREFACE

I suppose that this book was a twinkle in my eye when, in the spring of 1957, the editors of *Chemical Week* asked me to prepare a consultant's report on the Steroid Industry. The preparation of this report turned out to be a more adventuresome experience than I had bargained for.

I was, at the time, deeply immersed in the industrial effort to produce steroids and knew personally many of the prime movers in this area. In the following years, I came to know others. These were some of the most vital and interesting people one could encounter in any field of science and my discussions and visits with them were fascinating.

As originally planned, the report, which was to have been ready in six months, was to consist of 64 printed pages to be carried in three consecutive weekly issues. Actually, it took two years, and by that time the editors of *Chemical Week* pleaded that economy forced upon them by the recession of 1958 would allow them to print only a 16-page condensation.

It was Carl Djerassi who, after reading my completed report in the winter of 1958, suggested that I should expand it further and publish it as a book. This suggestion, coming as it did from one of the most gifted and serious savants in the field, proved irresistible. Now, more than three years later, I can acknowledge that this temptation led into what was for me an enormously complex and difficult undertaking.

Once I had decided to write a book, the big question that loomed was one of audience. I had not concerned myself with this question when preparing the report for *Chemical Week*. My audience here would obviously be the subscribers to the magazine, some of whom would read it and others would pass it by. Of those who might find it of interest, there would be businessmen, pharmaceutical executives, stockbrokers, some chemists, some teachers, and perhaps even an occasional biologist or clinician. What happened following the publication of the report in January, 1959, served only to astound and confuse me. I had letters and reprint requests from people who had never seen *Chemical Week* and whose interest in the industrial details of steroid production could not have been anticipated. The publishers of *Chemical Week* sold out their entire supply of 10,000 reprints, some to industrial organizations, but most to individuals in various fields not directly connected with steroid production. One request which came to me was from a professor of biochemistry at a medical school who wanted a reprint for each of his students.

I knew then that the potential audience for this book was large but also

heterogeneous. The question still remained, for whom was this book to be written? I resolved it by deciding to take the broadest approach that my experience would permit so that while no one reader would be totally satisfied, each might find some gaps filled in areas which were less familiar to him. Thus, I hoped the chemist might learn more about the intricacies of the biological exploration of steroids, while the biologist could provide himself with a guide to the maze of chemical reactions which makes possible this cornucopia of new compounds.

The clinician who in the end must use these products is, in my opinion, one of the most neglected victims of the flood of events that have occurred in steroid research. He is both wooed and abused with torrents of superficial information intended to get him on the bandwagon of the new wave of therapies made possible by steroids, but he is not credited with enough intelligence or interest to enable him to distinguish valid from invalid claims or to recognize that two or more competitive products may actually be the same compound, their differences residing only in their trade names. It is my hope that this book will spare the clinician the time and effort that would be required for him to gather from diverse sources the background material which would enable him to understand what the chemists and biologists are up to in their research on steroids. This understanding is essential if steroid drugs are to be used widely and well. At the same time, it is important for the chemist and biologist to be able to look over the clinician's shoulder so that they may understand the problems faced by the man who holds the key to the successful fulfillment of their efforts.

Finally, there are the businessmen, the pharmaceutical executives, the government officials who must make the decisions to spend research dollars, take the risks, and assess the rewards associated with this involved endeavor. These individuals must be in a position to look over everyone's shoulder and judge wisely. It is to their credit that so many "nontechnical" people have allowed themselves to become intrigued with the steroid potential and imbued with the adventuresome spirit of the research workers. To the extent that they have been able to understand what was going on, they have been willing to "stick their necks out." If this book helps them to understand more, I hope we will see them further out on a limb. Scientists are not the only ones capable of using good sense.

With the question of audience resolved, decisions concerning content were easier to make. I decided to put down what I knew about the chemical, biological, and clinical motivations in steroid research. To back up these opinions, I had to refer to a mountain of reference data which I had accumulated over the past sixteen years. These were sorted, charted, and analyzed with the help of my associates so that my statements could be as accurate and reliable as possible. Should the data itself be included in the book? It would make it heavy, unwieldy, and expensive. This decision was left to my publishers. They decided, and I think wisely so, that since

the information was at the time not available within the covers of a single book and had to be sought out, in each case, via numerous cross references, a useful purpose would be served by including the tables and catalogue of biologically active steroid compounds.

The decision to include the data concerning the relation between structure and function of the compounds created a formidable task, however. During the time required to assemble this information, history was being made almost daily, thus requiring constant revision of the textual material. Finally, it was decided that the catalogue of new compounds was to be cut off as of July, 1960; some exceptions were made in the case of important compounds revealed during 1961, after this deadline and while the manuscript was being put in final form.

I am certain that in the libraries of the larger companies engaged in steroid research, information about the biological activity of new steroid structures is readily available via computing machines and automated retrieval systems. Unfortunately, I did not have access to such facilities. I had to rely upon human hand and brain, and I feel that of necessity my compilation must be replete with human error. For the latter, I assume full responsibility, but credit for hands and brains must be shared with my indomitable associates who worked both fingers and brains almost to the bone. John Barbour did most of the compound classification; Bernard Schoen produced the chemical reaction flowsheets.

My wife Betty had the hardest job of all, spending the better part of two glorious summers at Fire Island discussing each phase of the manuscript and converting what was, at first, an undecipherable mess, into coded and comprehensible form.

If I ask to be excused for the human errors contained herein, I must also acknowledge the many human ingenuities contributed by good friends which helped to perfect the manuscript and make it more meaningful. For their painstaking efforts, I wish to thank Robert Snyder, Daniel Searle, and Frank Colton of G. D. Searle and Co.; R. S. Schreiber of Upjohn; Carlo Alberti of Farmitalia; Pietro de Ruggieri and Zoltan Korenyi of Ormonoterapia Richter; Alberto Ercoli of Vismara, Leon Rubin and Peter Ziegler of Canada Packers. James O'Connor, medical director of Philips Roxane, and Harry Rudel, medical director of Syntex, together with my associate C. B. (Bill) Taft, deserve special thanks for their assistance in perfecting the sections on progestational agents, central nervous system, bioassay methods, and miscellaneous applications of steroids. William Rubin of *Drug Trade News,* Joseph Kalish of *Drug and Cosmetic Industry,* and Vincent Marsilia of *Chemical Week,* provided invaluable advice on the editing of various sections.

My thanks also to Hans Selye, Thomas Dougherty, Alex Zaffaroni, Georg Rosenkrantz, A. Stanley Cook, Albert Wettstein, Kenneth Savard, Arthur Odell, Oscar Hechter, Vladimir Petrow, Francois Robinet, Gino

Bergami, Bruno Camerino, Robert Gaunt, Jerome Spellman, and my brother, Mort Applezweig, for their suggestions, reprints, and good wishes.

In the medical area, Rachmiel Levine was my most deliberate and abrasive critic. Even though my enthusiasm caused me, in some cases, to reject his strict cautioning, it was both inspiring and enlightening to discuss, word by word, the therapeutic implications of steroid drugs with this master clinician.

I am certain that I have neglected to mention many other individuals who were kind enough to read my manuscript and make suggestions here and there. I ask them to forgive me because it has been a long gestation period and my memory is crowded. I must not forget to thank Margaret Hoffman and Martha Levine of my organization who helped prepare and correct the various versions of the manuscript.

There are three individuals whose contributions to this book cannot be forgotten. Although they did not participate in reviewing the manuscript, their contributions were made many years ago when I first became interested in the steroid field. The first of these is Russell Marker. Working with him in the early days when the Mexican steroid industry was founded made me realize that he was probably the most remarkable chemist I would ever encounter. He worked without the aid of modern instruments, using only the "geographer's" intuition of the classical organic chemist to chart the intricate structures of the steroid sapogenins. As though this were not enough, he then turned with the same intensity to the commercial extraction and conversion of these compounds to sex hormones. It is difficult for me to understand why, after all these years, the Mexican Government has not seen fit to officially honor this man who single-handedly created an industry which has brought such wealth and prestige to their country.

My friendship with Percy Julian was another strong contribution to my interest in steroids. Although years and distances have often intervened, we have spent hundreds of hours together discussing research and industrial challenges which were made all the more adventuresome by the warmth and enthusiasm of this exciting man.

The most important influence of all was my close association with Steven Winkler. A businessman rather than a scientist, Steve had the foresight, the courage, and the persistence to struggle against all odds to make a success of the steroid dream. As manager of Laboratorios Gedeon Richter, he joined forces with Russell Marker to start a "backyard" industry which had only a prayer of a chance for success. When I first visited Mexico in 1949, Steven Winkler hired me as a consultant to his little enterprise, and this relationship continued until Diosynth was sold to Wyeth International in 1960. During these years of intimate collaboration, I came to admire the quiet strength and boldness of this good-humored man who risked his personal security and health on what he believed in.

As I was writing these words, I received the news of the untimely death of Steven Winkler on February 10, 1962. I mourn the loss of this gentle and important person who was my dear friend.

NORMAN APPLEZWEIG

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INTRODUCTION

Research into the chemistry, physiology, and pharmacology of steroids is a major preoccupation of the pharmaceutical industry. In other fields of research industry has been content to await and then adapt basic discoveries of the academic world, but steroid research has been carried out, almost from the very beginning, under the direct auspices of the drug companies. More time, money, and manpower are now being expended on steroid-oriented research, process development, and clinical study than on any other single group of drugs. Moreover, this concentration of effort and investment breaks all precedents in the history of the pharmaceutical industry. Are steroids the "sputniks" of present-day drug research? Does this field of investigation represent a never-ending source of new discoveries, products, and profits? This book will attempt some answers to these questions.

The compounds under consideration here—compounds made from not very accessible raw materials by techniques which must be constantly created anew—are among the most difficult substances ever to be handled on an industrial scale. Progress in this field comes at a high price. Structurally complex, physiologically capricious, steroids as a business risk are unpredictable. The one thing that can be predicted is that there is a great potential here, and every day nature provides more evidence that steroids are, as far as the body is concerned, wonder compounds. This is what leads the pharmaceutical industry into deeper and deeper commitments to this line of investigation.

Even the spectacular history of the discovery and exploitation of the antibiotics provides little basis for comparison. The antibiotic idea was a simple one for industry to comprehend. Once the principle was demonstrated by the discovery of penicillin, there seemed a straight path to follow. It was now known that, in the world of microorganisms, substances were produced by some species which were lethal to competitive species. It was not difficult to decide to exploit this principle by developing a technology for cultivating such organisms and harvesting the crop of new drugs through isolation of these natural chemotherapeutic agents. True, in doing this on the vast scale that it did, industry had to create ingenious new and highly specialized techniques; but the goal was always clear—antibiotics could be searched for in nature which would be useful to combat pathogenic invaders. Then, as resistant organisms developed or new diseases appeared, newer antibiotics would be sought for by "fishing in the same waters" with well-established techniques.

In the case of steroids the basic idea is exceedingly more complex, but also more challenging. Since the first revelation, less than 30 years ago, that steroid compounds were serving as the chemical messengers, or hormones, which controlled sex functions in mammalian organisms, and that slight differences in structure—a methyl group or a double bond—could mean the difference between maleness and femaleness, these molecules have been regarded with awe by physician, chemist, and industrialist alike. As a result of vigorous effort, the sex hormones were isolated, characterized, synthesized, and made available as drugs for the treatment of endocrine deficiencies and the modification of body functions. Even more important was the disclosure, as a result of continuing investigation, that steroid compounds played a role in numerous other physiologic networks. More than thirty steroid compounds were isolated from the adrenal cortex, which, physiologists believed, was the fountainhead of a control system over a myriad of cellular activities throughout the body. Thus inflammation, or the response of the cell to injury, the total metabolic response of the cell and, as eventually became evident, the over-all behavior of cellular systems, were found to be remarkably influenced by one or another of the steroid compounds isolated from nature or created in the laboratory. Here, then, was the lure which brought this great interest into being. Nature was showing the way, far in advance of any theories that man had been able to elaborate, to create chemical messengers which could regulate, control, arbitrate, and defend the various cellular systems so that their activities might contribute to a more harmonious functioning of the organism as a whole.

The Search for Biologically Active Steroids

Obviously, the challenge presented by the potentialities of steroid research is intriguing enough to capture the imagination of anyone who is interested in creating new drugs; but how does one follow this tempting path and where does it lead? In the early days of steroid product development, events were very much dictated by chance. One company would look into steroids in order to replace a gland extract product which had been made obsolete by new findings in endocrinology. Another would seek to develop a hormone product in order to complement other products it already had in this field. Still another, in this case a paint company, sought to exploit a by-product plant sterol and decided to learn how to convert it into sex hormones. Short-range projects were the order of the day, and justifiably so. The limited applications which could be foreseen for steroid compounds dictated caution and economy. So long as the effort was to duplicate natural hormones and use them for replacement therapy in a small number of human ills, the research objectives were relatively simple and not too costly. Today the situation has completely reversed itself. A race is on for these new drugs, and the competition is

keen. Today, for those who wish to exploit the steroid molecule, there is no alternative except wholehearted commitment to total research.

The steroid molecule consists of only four rings. Those steroid compounds found in the body which have hormone activity all possess this ring, and in addition, have a limited number of side groups with minor variations which give them tremendously different physiologic properties. Most of the natural hormones have a ketone at position 3 and a double bond between carbons 4 and 5. There is also a hydroxyl group or side chain at position 17 in the sex hormones and another hydroxyl group at carbon 11 in the cortical hormones. In most cases where these groups have been removed or altered, all known activity is lost or decreased. Some changes or additional groups introduced at other positions have produced modifications in the biological properties, and some of these new properties may be considered as quite remarkable.

While the combinations and permutations of the possible changes that could be introduced at these remaining positions are relatively large, there is somewhere a limit to the number of useful compounds which can be expected to emerge. On the basis of work done to date, it can already be anticipated that most of the new compounds which result will be useless, either because they are physiologically inert or because we do not yet possess the biological knowledge which would enable us to discern the potential usefulness of these new substances. What, then, are the odds in this game of "structural roulette"?

The Cortisone Era

The first large-scale commitment to cortical steroid research was undertaken by Merck & Co. during World War II at the behest of the government, as the result of an erroneous belief that the Germans were successfully using an adrenal hormone product to protect their fliers from the effects of high altitude. The successful synthesis of cortisone and later hydrocortisone by Merck made supplies available for trial in a number of diseases in which adrenal insufficiency was postulated. The discovery of the anti-inflammatory action of the natural cortical hormones in rheumatoid arthritis was a stunning and completely unexpected result of this research effort. With the sudden prospect of having to provide cortisone for millions of arthritic sufferers, other organizations were spurred into action, and the race to produce cortical steroids began.

Brilliant new techniques were created, new raw-material resources were found, and new concepts for the conquest of disease emerged. But the most important result of this massive research effort was that it destroyed the very premises which set it into motion. It turned out that cortisone was not the final answer. Arthritis was not due to adrenal cortex insufficiency. The millions of arthritics did not represent the assured outlet for this now abundantly available wonder drug. Instead, it was

shown that the adrenal cortex produced hormones which serve to counteract inflammation, regardless of its cause. Arthritis was an inflammatory condition of unknown cause whose severity could only be diminished by cortisone. Countless other distressing ailments, however, could also be reduced in severity by this compound. Furthermore, it became apparent that cortisone and hydrocortisone were not the ultimate answer. Modifications of these molecules, such as 9-fluorohydrocortisone, prednisone, and prednisolone, showed improved properties. Thus the research vistas were widened, so that the concern was no longer *how* to produce but *what* to produce.

Steroid Drugs

Since it had now been demonstrated that nature could be improved upon in this way, attention was also turned to other steroid hormones to see what could be done to improve upon them. The male sex hormone testosterone, which showed promise as a muscle-building agent and as a substance which might suppress the growth-stimulating properties of the female hormones in breast cancer, was modified so that its anabolic action was intensified while its masculinizing action was diminished. Likewise, the progestational steroid progesterone was improved upon so that its potential for maintaining pregnancy or preventing abortion was greatly increased; in fact, the new and more powerful progestogenic substances created offered promise of permitting complete control of the menstrual cycle so that conception could be prevented and fertility improved.

What about other possibilities? As we study the many biological actions of the various steroid hormones, it becomes apparent that these properties could be put to good use if they could be separated from the other, sometimes contradictory, actions of the natural hormones. So a search is on for "nonhormonal hormones": estrogens which retain the advantageous properties of counteracting the growth of prostatic cancer and the disproportionate accumulation of cholesterol in the male circulatory system, but which at the same time are deprived of the feminizing potency that prevents their continued use in male patients; modified androgens which will enable a premature infant or an ailing surgical patient to gain weight and build muscle or will restore a debilitated geriatric patient to vigor without excessive masculinization.

And what about new physiologic manipulations? Compounds to influence salt and water retention, potent diuretics, compounds to regulate heart rate, compounds to influence the nervous system, to sedate, tranquilize, or stimulate the brain—these are all within the realm of possibility. How many will be found and how much more is there to be looked for is no longer the question. There is now not a problem of quantity but one of quality. Completely new and hitherto undreamed-of effective drugs are being created by this effort to follow and improve upon nature's

physiologic utilization of steroid molecules. Here is the lead every research director looks for—one that is worth following because it has built-in promises which may help us exceed by far the goals to which our present-day knowledge permits us to aspire.

Plan of This Book

One way to achieve understanding of the problems and promises of steroid research is through examination of the intricate history of the drug industry's preoccupation with these compounds. Here will be found an extraordinary example of collaboration and mutual interdependence of basic research and applied technology. By following this thread, it is hoped that a picture can be developed which will be comprehensive and at the same time permit certain economies in presentation and style.

The purpose of this book is not to itemize but rather to explain and correlate the multidisciplinary efforts that have gone into steroid research, and to report on the progress that has been achieved by this collaboration.

Excellent reference works on the chemistry and physiology of steroid compounds already exist. No attempt will be made to duplicate the extensive and detailed reviews available in such books as *Steroids,* by Louis and Mary Fieser, *The Hormones,* by Pincus and Thimann, or in the annual volumes of *Recent Progress in Hormone Research, Vitamins and Hormones, Annual Review of Biochemistry,* and *Annual Review of Physiology.* Discussions of proof of structure and reaction mechanisms have been deliberately omitted, as have been innumerable references to individual authors whose collective contributions have made the history sketched briefly in this book. A summary of progress in the development of biologically active steroids is presented instead, some of it in the form of charts of production processes and lists of new compounds. References to the chemical, biological, and patent literature have been included wherever possible in these lists.

For purposes of exposition certain of the outstanding physiologic postulates and their experimental verifications have been used illustratively. Many pertinent references, while not specifically discussed, will be found grouped by subject at the end of individual chapters.

Part One
HISTORY AND BACKGROUND OF STEROID PRODUCT DEVELOPMENT