

Symposium on
Steroids
in
Experimental
and Clinical Practice

Edited for the Committee on Arrangements

by

ABRAHAM WHITE



1951

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Preface

In June, 1950, a group of individuals, later constituted as the Committee on Arrangements, was requested by I. V. Sollins of the Chemical Specialties Co., Inc., to discuss the feasibility of a conference dealing with steroids in experimental and clinical practice. Conversations among the Committee members led to general agreement that it would be of advantage to have the proposed conference evaluate the laboratory and clinical experiences with the 11-desoxy steroids, particularly inasmuch as several recent symposia and meetings had been concerned with the 11-oxysteroids, notably 11-dehydro-17-hydroxycorticosterone. Accordingly, plans were formulated which resulted in the First Annual Steroid Conference, held in Cuernavaca, Mexico, January 15-18, 1951. The invited speakers and guests were informed that the papers delivered at the conference, as well as the discussion, would be assembled for publication in book form. Each discussant was provided with the opportunity of editing his comments. Frequently, the discussion occurred following presentation of a group of papers, and in these instances the comments have been assembled following the last paper in the group.

The Committee on Arrangements requested the undersigned to function as editor of this volume. All of the material presented at the symposium has been included. There are a few differences between the order of the papers and discussions as printed and as presented orally; these alterations were made after discussion with, and approval by, the Committee on Arrangements. Little effort has been made to standardize the style of the manuscripts, particularly bibliographies, inasmuch as it seemed desirable to limit the extent of editorial changes in order to expedite prompt publication. In addition to the papers and discussion presented at the symposium, there are included five tables, which have been added at the end of the book. It was the opinion of the Committee on Arrangements that these tables might serve as a type of compound index, enabling the reader to ascertain quickly the salient information relating to the clinical investigations in this volume. In a sense, these tables represent a guide for summarizing the clinical studies presented at the symposium, and provide material from which the reader may formulate an opinion regarding the present status of the 11-desoxysteroids in clinical practice.

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Introduction to the Symposium

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This Symposium on Steroids in Clinical and Experimental Practice will be, it is hoped, the first of a series of annual meetings established solely for the purpose of enabling and stimulating a free and unlimited exchange of information among clinicians, chemists, and biologists who are interested primarily in the general field of endocrinology—its chemistry, its physiology, and its clinical applications. With this thought in mind, the present symposium program in Cuernavaca was organized around the theme of the 11-desoxy steroids as a class.

Thus, the specific tasks of this first Cuernavaca conference are to study and ascertain the present status of 11-desoxy steroids in animals and man; to relate and integrate data obtained from various independent clinical and experimental studies concerning each individual steroid compound under investigation; to recommend further research along indicated lines with individual steroids or groups of compounds on the basis of the correlated data developed during these meetings; and to evaluate, if at all possible, the present or future clinical applications of such compounds. These tasks are not easily accomplished, for it is evident from the outset that existing knowledge concerning the pharmacology and metabolic or clinical activities of the 11-desoxy steroids is sparsely developed in some instances, heavily weighted by preconceived clinical opinions in others, and confused by seemingly contradictory information or inadequate studies in still other instances. Obviously not all these fragments of knowledge will be pieced together at this meeting, nor will all the confusion be dispelled. But at least the discussions to follow should produce some degree of agreement as to the nature of the problem, some common approach as to future investigations, and some immediately realizable although perhaps limited recommendations as to the clinical usefulness of many 11-desoxy steroids.

There is, of course, a substantial accumulation of knowledge concerning the classical sex hormones and desoxycorticosterone, all members of the 11-desoxy series; but of the hundreds of naturally occurring or newly created members of the 11-desoxy steroid family, almost nothing is known of their metabolic transformations or possible clinical applicability. This lack of knowledge concerning the 11-desoxy steroids applies

as well to all but one of the related 11-oxygenated compounds, namely, cortisone. However, here the dramatic impact of cortisone upon investigators and public alike plays a role. Without doubt, since the first announcement of cortisone's effectiveness in arthritis, there has been an overwhelming rush of activity on the part of investigators to study this 11-oxy steroid in scores of clinical or experimental conditions. More recently it has been realized that some of the other 11-oxy steroids, such as Compounds B, D, and F should be studied with equal intensity. Unfortunately, except in a few institutions, similar emphasis has until now not been given to the study of the 11-desoxy steroids, with the result that possibly beneficial or useful properties of some of these compounds may be overlooked. This conference can and should contribute the stimulus for intensive study of the hundreds of steroids in the 11-desoxy category. If it does this, it will have made a major contribution.

For the past two years, and more especially during the last year, the Syntex-Chemical Specialties organization which sponsored this meeting has very actively supported a program for the clinical and the biological investigation of the 11-desoxy compounds. The organic chemists of Syntex have synthesized literally hundreds of previously unknown compounds as well as scores of compounds that were previously known but until now available only in micro quantities. These steroids were distributed, without charge, in amounts ranging from a few grams to thousands of grams to investigators in many institutions for study in animal or in human subjects. There has always been only one restriction or stipulation, namely that these compounds be used and not be left sitting on laboratory shelves. Many investigators present here have benefited by this research program, and perhaps many more will benefit in the future, for it is intended to continue and extend such support to steroid investigation.

At this point it is perhaps appropriate to add that although the Syntex organic research program was for a time mainly concerned with the synthesis of 11-desoxy steroids from Mexican plant source materials, it has more recently also undertaken the synthesis of 11-oxy compounds from similar source materials. These studies have already resulted in the synthesis and production of several compounds in the 11-oxygenated series. In the near future some of these will be made available for research in the clinical field.

However, the Syntex group has in the past, and will continue in the future, to emphasize the advantages of the 11-desoxy compounds. They are available for clinical investigation in far greater quantities than are the 11-oxy steroids. They are far less costly to produce, since the vegetable sapogenins from which they are synthesized are abundant. Inasmuch as so little is known as to the possible clinical value of all steroids, it is indeed logical to investigate intensively those steroids that can be made available in large amounts, after their activity has been proved, rather than to concentrate research on compounds which presently or in the

foreseeable future can only be obtained in rare amounts and at uneconomic costs.

Perhaps one additional reason may be advanced for this present conference in Cuernavaca. It is highly essential to resolve some of the discrepant and often contradictory reports that have been obtained concerning various 11-desoxy steroids presently being utilized in clinical practice. For example, certain clinicians have observed and reported the value of pregnenolone in rheumatoid arthritis. Others either have not observed similar effectiveness or perhaps have employed different criteria in the measurement of clinical results. Perhaps conditions of treatment, such as dosages, routes of administration, length of treatment, or form of the compound have varied; the fact is that discrepant reports have appeared.

The same situation applies to reports concerning the clinical usefulness in arthritis of testosterone, other sex hormones, and some of the corticosteroids. Furthermore, similar problems also are present in evaluating steroid therapy in many other clinical entities ranging from collagen diseases to cancer. It is hoped, therefore, that such problems would be discussed adequately at this meeting and that suggestions would be forthcoming for means of resolving at least a few of these apparent differences.

The program of this conference provides for an emphasis on pregnenolone because this compound has been widely employed during the past year and because pregnenolone is a cheap, plentifully available, and perhaps clinically useful compound. However, the program proposes to raise various questions not only with respect to pregnenolone but also to other compounds about which conflicting or ambiguous clinical or biological data have been obtained. It is to be hoped that in the discussions and evaluations to follow, the members of this conference will attempt to equate data in terms of comparable units, i.e. patients of similar age, sex, and progression of disease; similar diagnostic standards and criteria of therapy; equal dosage levels for equal duration of therapy; similar routes of administration and similar pharmaceutical dosage formulations; as well as many other factors that govern an experiment, whether it is clinical or biologic. There would seem to be rather obvious precautions to employ in objective evaluation of new drugs, and yet perhaps because of their obviousness it is not surprising to find that much of the published literature pertaining to the subject shows the absence or disregard of these equating considerations. There has been a marked tendency for certain investigators to write off a number of steroids as completely useless on the sole basis of inadequate comparisons. This conference can correct such mistakes.

When the idea of this meeting first arose, some six or eight months ago, the counsel of Drs. Reifenstein and Pincus was sought. After preliminary conversations with and advice from these workers, an Advisory or Arrangements Committee was organized from among scientific workers in Mexico and the United States. This committee planned, or at least counseled in the planning, of the program that now constitutes the