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CLINICAL USES OF ADRENAL STEROIDS

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FOREWORD

This volume is one of a series being published by the Blakiston Division of McGraw-Hill based on postgraduate symposia and courses offered by the Division of Continuing Education in Medicine and Health Sciences at the University of California (Los Angeles), School of Medicine.

Since it is the policy of this department to offer seminars and symposia on current topics in which there is new diagnostic or therapeutic material available, it seemed highly desirable to have the proceedings edited and published. The merit in this approach to medical publication has been amply demonstrated by the reception of previous volumes: *Clinical Disorders of Fluid and Electrolyte Metabolism*, edited by Morton H. Maxwell, M.D., and Charles R. Kleeman, M.D.; *The Differential Diagnosis of Abdominal Pain*, edited by Sherman M. Mellinkoff, M.D.; *Modern Dermatologic Therapy*, edited by Victor D. Newcomer, M.D., and myself; *Management of Medical Emergencies*, edited by John C. Sharpe, M.D.; *Treatment of Emotional Problems in Office Practice*, edited by Frank Tallman, M.D.; and *Sterility*, edited by Edward T. Tyler, M.D.

We feel that these volumes of the UCLA Medical Extension Series, of which this is the seventh, will be of practical value to the physician who wishes to have at hand a general coverage of the subject with which he is concerned.

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PREFACE

Since September 21, 1948, when the first injection of cortisone crystals was given by Dr. Philip Hench to a patient with rheumatoid arthritis, there has been an unprecedented development in the use of corticosteroids in clinical practice. During this period cortisone or chemical variants of it have been tried in literally all diseases known to affect man. Many new analogues of cortisone and cortisol (hydrocortisone) with varying physiologic potency and biologic effect have been produced in the laboratory. These have been studied with a variable degree of thoroughness in the clinical situation. Today differing opinions still exist about the value of the corticosteroids in many clinical conditions in which they have been used. In spite of these inevitable conflicts of opinion, there is merit in periodically reviewing such an important and changing subject, for no compendium covering in detail all phases of corticosteroid therapy has been published in the English language since the development of the cortisone analogues. Furthermore, it is felt that the initial wave of therapeutic overenthusiasm has passed and that the relatively long-term beneficial effects and hazards of these agents can now be viewed with some degree of perspective.

From the commercial point of view, the corticosteroids are "big business." In 1958 they ranked fourth among the ethical "best sellers," with 95 million dollars' worth of sales for American pharmaceutical manufacturers. At present a feverish race is going on in the pharmaceutical research laboratories to synthesize newer and better analogues. New compounds are being turned out at such a rate that clinical or even animal testing is virtually impossible for all of them. The objective is, of course,

to prepare compounds that possess specific desirable physiologic action with minimal or no unwanted "side effects." The physician is deluged with medical advertisements and deafened by the pronouncements of pharmaceutical "detail men" who claim that one of the new corticosteroids is the answer to all his hopes. Unfortunately none has fulfilled these promises, although a reduced tendency to sodium and fluid retention has been one dividend. The most one can say is that each new analogue marketed has been more potent, milligram per milligram, than its predecessor. In the individual patient, however, this is meaningless, for at a comparable dosage level each analogue induces about the same number and degree of undesirable reactions. During the preparation of this volume three additional analogues were synthesized and have received clinical trial: betamethasone, fluprednisolone, and paramethasone. They are listed with their relative activities in Table 15-1 (page 344). Preliminary information suggests that they are anti-inflammatory agents with equivalent side effects but that they bear no clear advantages over other, more familiar non-salt-retaining corticosteroids.

There are, of course, distinct clinical indications for the use of corticosteroids, and they have saved many lives. Dr. Hench insists that one of their primary uses should be as "investigative weapons" for the study of normal and abnormal physiology. He has been overruled, however, by the enthusiastic acceptance of these hormones from the moment they were announced to the medical profession and to the public. One can hardly believe that there is a justifiable need for as much of the currently available adrenal steroids as is dispensed each year to the sick and not-so-sick. This view is implied by most of the authors of these chapters by their relatively restricted lists of "definite" indications and their far more extensive lists of disorders in which the indications are "relative" or nonexistent. Another concern of the contributors is the significant incidence of side effects, or, more appropriately, the physiologic effects of overdosage. These apprehensions have made themselves known in various ways in the individual chapters, and it is the hope of the editors that a some-

what more objective and moderate view will be taken by physicians who use corticosteroids. The constant danger of infection in patients taking corticosteroids must be kept in mind—the resistance to spread of infectious agents is reduced and the manifestations of infection are hidden by the anti-inflammatory properties of these hormones. Any suggestion of infection must be investigated and promptly treated. The other physiologic effects of corticosteroids must be constantly in the physician's mind—peptic ulcers, osteoporosis, diabetes, and mental disturbances.

Each chapter is written by an expert with wide experience who has given his considered and thoughtful advice and specific guidance on the use of corticosteroids in the diseases he discusses. Where appropriate throughout the book, the editors have summarized for easy reference in block form pertinent factors about the disorder under discussion or the therapy thereof. The blocks only emphasize certain important features. They are not uniform, nor do they provide a detailed summary of the subject material which they accompany. Furthermore, the traditional initial chapters on the physiology and biochemistry of the adrenal steroids appear at the end of the book, and clinical considerations are discussed beginning with Chapter 1.

With these innovations it is hoped that this volume will be a practical guide to constructive use of the various corticosteroid hormones in clinical medicine.

The original stimulus for the formulation of this monograph was a 2-day symposium held in Los Angeles in 1959. Most of the contributors to this volume took part in this symposium. In a few instances a discussion of a topic not covered in the symposium was solicited from an authority on the subject. The editors wish to take this occasion to express their gratitude to each of the authors who, despite pressing daily obligations from many quarters, has taken the time and interest to contribute his wisdom and guidance to this volume. The editors likewise can claim little credit for the wealth of material and advice that is presented herein, since that belongs in large measure to each of the contributors.

Sincere gratitude for assistance in preparing selected portions of this book is extended to Drs. Augustus S. Rose and Louis Rosner. Also, we are grateful to the Merck Sharp & Dohme Company for assisting and encouraging the original symposium, and to Lyvonne Kennedy and Ruth Hirsch for their help in preparing and editing the manuscripts.

Josiah Brown, M.D.

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CORTICOSTEROIDS IN PERSPECTIVE¹

I shall try to present a long-range view of where we stand in regard to the use of the steroids. How much has been accomplished? How much more needs to be done? How can we best proceed? Who should assume responsibility for our progress in evaluating the position of these powerful substances in clinical therapy?

The first question we posed at the beginning of this symposium was: "Are the steroids useful?" It is now clear that they are; indeed, you would probably not have attended the present discussion if you had not felt that they were. But this answer is too general. In each of the special clinical fields the answer varies; indeed, it changes from one observer to another and from one disease to another. The steroids may be lifesaving in certain diseases and destructive in others. Our problem therefore is to define the situations in which they are useful.

My first reaction in being confronted with this question is to be thankful that most of my decisions regarding the adrenal steroids are made in the laboratory or with regard to patients who

¹ A summary statement given by Dr. Bondy at the end of a 2-day symposium on the uses of adrenal steroids held in Los Angeles, Calif., 1959.

have clear-cut adrenal disease. These are two situations where the questions are easily answered. In the laboratory it is possible to control most of the variables so that the effects of steroids can be examined uniquely. In patients who are suffering from deficiencies or excesses of adrenal function, manipulating steroid therapy and withdrawal is relatively simple. I doubt that any physician will deny that adrenal insufficiency must be treated by the administration of amounts of hormone adequate to replace the missing secretion or that, when the adrenal is hyperactive, the proper approach is to reduce (by any of several maneuvers) the excessive activity of the gland. These are not areas of controversy.

There are other situations where years of previous experience have shown that the natural course of a disease leads inexorably to early death and where control of the disease represents clear evidence that the medication is effective. Patients who are about to die with diseases such as pemphigus or acute leukemia often improve in a most impressive fashion when steroids are given. Obviously, therefore, steroids are useful in treating these diseases. However, the fact that one steroid or another is effective is not really the complete answer to our problem, for we still must seek the best type of steroid and the best dosage schedule.

When one considers the diseases which are probably not really controlled by the steroids but in which suppression of symptoms may occur while the basic pathologic process continues to progress, the situation is much less clear. Are steroids really useful in the treatment of rheumatoid arthritis, or rheumatic fever, or ulcerative colitis? Here the answer is confused, for the progress of these diseases is variable and difficult to predict, and the course is so long that temporary successes may obscure long-term failures.

Finally, there are situations where steroids are probably harmful, such as infectious diseases, but even here clinical impressions have been recorded of a beneficial result in certain circumstances.

All these problems have already been discussed by my colleagues. All of them have reported time after time: "We don't

really know whether the drugs are useful." "We are not sure whether prednisone is better than cortisone, and whether dexamethasone is better than either of them." "We are not sure of the best dosage schedule for the treatment of this disease." Why does this confusion reign? After more than ten years of use, why are so few solid clinical data available?

Part of the trouble is the fact that there is no easy way of obtaining this sort of information. When, for example, a new steroid is introduced into clinical practice, a good deal of information based on laboratory investigation is available. It is relatively easy to arrive at an evaluation based on this type of information, because the answers can be obtained rapidly under rigidly controlled conditions. Unfortunately, there are very sharp limits to the type of information which can be obtained by such studies. For example, let us review the potency ratios which were presented by Dr. Roberts earlier in the session. You will remember that he was able to rank the various corticosteroid products in the order of their relative potency in altering electrolyte as compared with carbohydrate-protein metabolism.² But these data are difficult for the clinician to interpret and apply. This does not mean that the ratios are incorrect but that they refer to very restricted types of experiments, set up in an arbitrary fashion, in which steroids were given for a certain period of time to certain types of animals with certain salt loads and fed certain diets. Although these variables (as well as others) have been so standardized that the potency ratios he presented can be obtained reproducibly, it does not necessarily follow that the same ratio would be obtained if the situation were altered slightly. What would happen, for instance, if sodium were restricted, or if potassium were forced, or if the animal received the steroid intravenously rather than orally, or if the duration of steroid treatment were doubled? In each of these situations the potency ratios would probably change, and might change greatly. The ratios are, therefore, arbitrary figures. They are the best figures we have, and they give us a fair idea of what is going on, but they may

* These data are shown in Table 15-1.

not be directly applicable to clinical situations. As evidence of this, Dr. Kleeman has pointed out that patients who have been given very large doses of dexamethasone may retain sodium in spite of the fact that all the sodium balance studies done in animals have shown that this substance either has no sodium-retaining effect or that it is actually natriuretic. Comparable remarks might be made about laboratory studies of the actions of each of the corticosteroids.

Does this mean that any attempt to evaluate the actions of the steroids is futile? Clearly not, for a few—pitifully few—studies *have* been performed in the clinic under circumstances which lead to definite, scientifically acceptable conclusions. We have heard of the excellent controlled studies of the effects of cortisone on the course of ulcerative colitis, and you are all familiar with the joint British and American study of the effects of the steroids on the progress of rheumatic fever. Each of these studies was distinguished by certain important qualities. The patients were separated into unselected groups; the group which received the medication was balanced by a comparable control group which received some other type of treatment—placebo or potentially useful treatment such as aspirin in rheumatic fever. The data were obtained by observers who were impartial because they did not know how the patients had been treated. In summary, a controlled experiment was done using the double-blind method of controlling the enthusiasm of the scientist as well as the placebo effect of the medication on the patient.

The few such studies which have been carried out have demonstrated their value. In spite of “clear clinical judgments” to the contrary, it turns out that in rheumatic fever cortisone has little or no advantage over aspirin (which is much cheaper and safer).³ It appears that, in spite of the impression produced by uncontrolled observations, cortisone does *not* increase the incidence of intestinal perforation in ulcerative colitis.

I have emphasized these two studies to try to impress on you

³ A more recent study (see Chap. 5) indicates that corticosteroids are of value when given *early* in rheumatic fever.