SAFE USES OF CORTISOL

Third Edition

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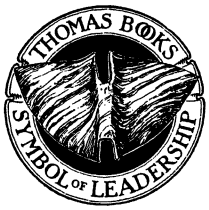

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PREFACE

In the seven years that have elapsed since *Safe Uses of Cortisol*, Second Edition was published, an important question that was raised at that time has been answered. We now know that the influenza virus attacks the human body by impairing the production of adrenocorticotropic hormone (ACTH), which, in turn, impairs the production of cortisol, the only hormone that is absolutely essential for life. We also now have reasonable explanations for some other vicious aspects of the "Terrible Influenza Epidemic of 1918" that was described so vividly by Gina Kolata in her excellent book, *Flu: The Story of the Great Influenza Epidemic of 1918 and The Search for the Virus That Caused It.* A few typographical errors that may have been confusing in the second edition have also been corrected.

In the past two years, a new infection has developed in central China and labeled Severe Acute Respiratory Syndrome (SARS). It is reportedly caused by a novel coronavirus and it has received much attention in the news media, but I have seen no reports of studies of its etiology. It has apparently spread worldwide through air traffic, with significant outbreak in Toronto, Canada, and scattered cases in the United States.

PREFACE TO SECOND EDITION

In the fourteen years that have elapsed since *Safe Uses of Cortisone* was first published, none of its statements, which seemed so contrary to popular and accepted ideas at that time and still are considered radical by many, have been disproven. On the contrary, many physicians have found the therapeutic recommendations helpful, and important aspects of the theoretical rationale for the effectiveness of safe, physiologic dosages of cortisone or cortisol in patients with chronic allergies, autoimmune disorders and the chronic fatigue syndrome have been confirmed and extended by reports from medical centers in both Europe and America. The therapeutic implications of these reports have apparently not been recognized, however. Furthermore, package inserts for cortisone and cortisol still do not differentiate between the effects of physiologic versus pharmacologic amounts of these normal hormones, implying that any dosage might produce any of the grim side effects that occur only with the administration of excessive amounts!

The dynamic nature of cortisol responsiveness undoubtedly contributes to this problem, since a dosage that is necessary for survival at times of increased stress may cause serious side effects if continued after the stress has subsided or if it is given at times when stress is not present. Similarly, if the dosage is changed capriciously, more harm than benefit may ensue. It is therefore important for practicing physicians to understand and to bear in mind certain important aspects of cortisol actions and effects that are discussed in Chapter 4, the title of which has been slightly changed to "Generally Accepted Uses of Physiologic Dosages." The title of the book has also been changed to *Safe Uses of Cortisol*, since cortisol is the glucocorticoid normally produced by the human adrenal cortex and cortisone must be converted to cortisol before it can produce its characteristic beneficial effects. Unfortunately, many continue to call all glucocorticoids "cortisone," which just adds to the confusion.

None of the statements regarding the background and the beneficial therapeutic effects of safe, physiologic dosages of cortisone or cortisol have been changed from the first edition because they are still valid, but further experience has confirmed and extended some of the impressions, and recent improvements in the diagnosis and understanding of the rationale for treatment of patients with mild adrenocortical deficiency associated with chronic allergies, autoimmune disorders and the chronic fatigue syndrome have been added. Because of their well-known reputation as dangerous drugs, however, and because patents on cortisone and cortisol expired over thirty years ago, these safe uses will probably not receive the promotion and advertisements that usually accompany effective new uses of a medication, but hopefully the improvement achieved by this type of therapy will be sufficient to enable it to reach medical textbooks eventually.

Because cortisol is such a dynamic hormone, with production and utilization fluctuating from minute to minute depending upon degree of stress as well as upon diurnal variation, the assessment of adrenocortical function cannot be as exact as the measurement of function of most other glands, but the combination of measurement of plasma levels of cortisol and of adrenocorticotropic hormone (ACTH) with Cortrosyn stimulation tests will identify most disorders encountered clinically. It should be remembered, however, that tests within the normal range do not rule out the possibility that administration of small, physiologic dosages might be helpful, so therapeutic trials might still be indicated. This may be related to the inexactness of the recorded normal range and to the evidence that cortisol can affect uptake by cellular receptors.

One of the more exciting developments during the past 14 years has been the elucidation of a relationship between the hypothalamus, the pituitary and the adrenals (the HPA axis) in responses to stress and infections and in the development of autoimmune disorders, so this will be discussed in the chapters on these disorders, especially since this relationship supports the rationale for the prolonged use of small, physiologic dosages of cortisol in their treatment. Now that rheumatoid arthritis has been found to be associated with a defect in response of the HPA axis associated with low blood cortisol levels, especially after stress, the rationale for the prolonged use of physiologic dosages of cortisol in this disorder makes it advisable for practicing physicians to be aware of the availability and safety of this type of therapy for these patients as well as

for patients with other autoimmune disorders, chronic allergies and the chronic fatigue syndrome.

The elucidation of the effects of various intracellular messengers such as cytokines has stimulated research on the possible use of these agents in the treatment of disease, but because the entire immune process seems to be regulated by the HPA axis, the ability to provide proper amounts of cortisol is a major factor in the maintenance of normal energy, normal immunity and normal health and one that might be more effectively and more economically approached today.

The chapter on the treatment of ovarian dysfunction and infertility maintains its prominent place in the book because, when properly administered, safe physiologic dosages of cortisol still seem to be the most effective as well as the most physiologic and least expensive treatment for these disorders, and also because the use of physiologic dosages of cortisol in patients with these conditions first revealed their effectiveness and safety in the treatment of allergies, autoimmune disorders and unexplained chronic fatigue. The recent publicity and concern regarding the difficulty of increasing numbers of couples in achieving pregnancies and the occurrence of unwanted multiple pregnancies in many women treated with currently popular therapeutic programs emphasizes the potential value of this therapeutic approach that tends to restore normal ovarian function and fertility instead of artificially stimulating ovulations.

Because standard medical texts do not discuss mild adrenocortical deficiency and in their discussions of treatment of more severe degrees of adrenocortical deficiency they often suggest the use of stronger derivatives of cortisone or cortisol, such as prednisone or dexamethasone, practicing physicians should find the description of the use of small, physiologic dosages of cortisol in this book especially helpful.

There will undoubtedly be those who think that the use of the currently more popular and stronger derivatives of cortisone or cortisol on a once or twice daily schedule will be equally effective, but nature usually has good reasons for her choice of agents participating in the physiology of life, so it seems preferable to administer natural hormones, especially for long term use and when treating deficiencies of these hormones. Hence, a schedule of administration that mimics the normal production pattern of cortisol as closely as is feasible seems advisable. Furthermore, the effectiveness and safety of this program of treatment has been

clearly demonstrated in over one thousand patient years of experience, during which over 200 babies have been born to women taking small, physiologic dosages of cortisol or cortisone acetate throughout their pregnancies and postpartum periods with no evidence of harm to either mothers or babies. On the contrary, evidence that this treatment has helped to prevent miscarriages and postpartum depression or thyroid disorders has been impressive. Since this type of therapy was initiated over thirty-five years ago, many of these babies have now reached adulthood, still without any evidence of abnormality. These observations should not be surprising, since this type of treatment tends to restore normal function rather than to alter or impair it.

There also will probably be those who are concerned that double blind placebo studies have not been used in evaluating the therapies utilizing physiologic dosages of cortisol. There are two reasons for this: First, the dynamic nature of adrenocortical function would make it difficult if not impossible to devise studies in which a constant dosage of cortisol for a specific period of time to a number of patients would provide a suitable test of its efficacy. Second, the continuing emphasis by leading medical journals on the importance of double blind studies is surprising, since the cause of the placebo effect has never been elucidated. Because the placebo effect implies an expectancy by the patient for improvement resulting from the treatment being studied, which in turn might make the patient feel less stressed and thereby decrease the strain on his or her adrenals, the possibility that the placebo effect might result from improved adrenocortical function should be studied. Furthermore, the effects of other hormones have never required double blind placebo studies, and the beneficial effects of small, physiologic dosages of cortisol are usually so clear that this type of confirmation has not been considered necessary.

My retirement from the faculty at Case Western Reserve University in 1980 at the age of 65 years, plus the retirement of referring physicians who were familiar with the cortisone story and with my work, mostly obstetricians, gynecologists and allergists, decreased my opportunities to extend the clinical studies that were the basis for the first edition of this book, but I have been able to continue to follow a few patients, and the University of Virginia School of Medicine, from which I graduated in 1940, has enabled me to continue part-time research and writ-

ing through my appointment here as a Clinical Professor of Internal Medicine.

Finally, it is hoped that this type of therapy will not only be helpful in the treatment of patients with the various disorders mentioned, but also that it may lead to a better understanding of the factors that contribute to the development of these disorders and, hence, ultimately contribute to their prevention.

PREFACE TO FIRST EDITION

The potential of cortisone and hydrocortisone in clinical medicine has been confused by numerous factors. When agents that initially were thought to provide one of the greatest advances in therapy in the history of medicine were found to be capable of causing numerous serious and sometimes catastrophic side effects, both physicians and patients understandably reacted with alarm. Unfortunately, the reaction was so great that perspective has been lost. Furthermore, misunderstanding has resulted from failure to differentiate between physiologic and pharmacologic dosages and effects, from confusion of natural steroids with more potent derivatives, from a lack of knowledge of the nature of beneficial effects, and from other, more subtle factors.

Cortisone and hydrocortisone (cortisol) are natural hormones and, when properly administered, are as safe as any other naturally produced hormones. In addition to its primary role in response to stress of any type, hydrocortisone has beneficial symptomatic effects in many diseases of humans, but its use has been limited because of fear of the harmful side effects that may occur with the pharmacologic dosages that have been customary.

With a thirty-year background of experience with clinical uses of cortisone and hydrocortisone, the author reviews the cortisone story from its beginnings and presents an optimum program of administration of safe, physiologic dosages in adrenal insufficiency and congenital adrenal hyperplasia. Employment of safe dosages on a proper schedule has demonstrated a promising potential in patients with gonadal dysfunction with or without infertility, rheumatoid arthritis, allergic rhinitis, asthma, recently recognized autoimmune disorders such as hyperthyroidism with diffuse goiter, chronic thyroiditis, and diabetes mellitus, and common clinical problems such as functional hypoglycemia, hirsutism, acne, and chronic cystic mastitis. The relative frequency and

clinical significance of low adrenal reserve as a cause for unexplained chronic fatigue or functional hypoglycemia and as a possible contributing factor in many allergies provides another area of therapeutic promise. Recent evidence regarding the mechanisms of physiologic effects of hydrocortisone is discussed in relation to these areas of clinical potential.

INTRODUCTION TO FIRST EDITION

The adrenals are a major component of the body's defense against stress, and this includes any type of injury or infection. The malaise associated with any severe injury or illness can be alleviated by the administration of suitable doses of adrenocortical hormone. It is apparent that the secretion of a gland that has such remarkable potential may affect the body's reaction to any unpleasant condition, whether physical or psychological, injury or disease. Hydrocortisone is the most important of the hormones produces by the adrenal cortex. Cortisone is converted to hydrocortisone after absorption, hence its effects are qualitatively the same. Unfortunately, when cortisone was first introduced to clinical medicine, the amount of this hormone that was normally produced by human subjects was not known, nor was an optimum route or schedule of administration. Furthermore, under some circumstances the administration of a large dosage of either cortisone or hydrocortisone might be dramatically beneficial; under others, the same dosage might cause great harm. This combination of properties has resulted in much confusion regarding the therapeutic usefulness versus toxic potential of these steroids in clinical medicine.

While I was a student and house officer at the Massachusetts General Hospital, 1939 to 1942, I was fortunate to have Dr. Fuller Albright as an instructor. Dr. Albright was a pioneer investigator of the function of the adrenal cortex in humans, and he stimulated my interest in the relationships of the adrenals and other endocrine glands to stress. During World War II, while serving as a flight surgeon in India, Burma, and China for two and a half years, I had an opportunity to observe the effects of intense psychological and physical stress on airmen.[1] Subsequently, I spent two years on a research fellowship with the Thyroid Clinic at the Massachusetts General Hospital under Dr. James Howard Means and a year with the Endocrine Clinic under Dr. Albright.

In early 1949, Dr. Albright received a small supply of Compound F,

the adrenocortical steroid that was later to be called hydrocortisone or cortisol, for clinical studies. Dr. Philip Hench and his associates at the Mayo Clinic had recently reported impressive beneficial effects of cortisone acetate and adrenocorticotropic hormone (ACTH) in patients with arthritis,[2] and Dr. Albright decided to determine the effects of Compound F upon metabolic balances in a human subject. Drs. Paul Fourman and Frederick Bartter collaborated with him in the study.[3]

Meanwhile, I had been invited to take charge of the Endocrine Clinic and Endocrine Research Laboratory at University Hospitals in Cleveland, Ohio. Shortly after my arrival in the summer of 1949, I received a supply of cortisone acetate from Dr. Elmer Alpert of Merck, Sharp and Dohme, Inc. and of adrenocorticotropic hormone (ACTH) from Dr. John Mote of the Armour Laboratories to use for clinical investigation. Later the Upjohn Company provided a generous supply of cortisone acetate and hydrocortisone for clinical studies. When cortisone acetate and hydrocortisone became available for general clinical use in 1950, I was delegated to see every patient given either of these agents at University Hospitals for over a year, and most of such patients subsequently. This experience provided a perspective of the beneficial and the harmful effects of the clinical uses of these agents, and in 1955 I summarized the current status of their use in clinical medicine.[4]

At this time I became intrigued with the beneficial effects of small doses of cortisone or hydrocortisone in women with ovarian dysfunction and infertility. As a result of my previous experience with the duration of effects of hydrocortisone and with the treatment of patients with spontaneous adrenal insufficiency (Addison's disease), I had patients divide the daily dosage so that a portion was taken before each meal and at bedtime. The results of this work were published, but patents on cortisone acetate and hydrocortisone were terminating, and the medical profession and general public had become disenchanted with these agents because of the toxic effects that occurred with larger dosages.

As I continued clinical studies with safe, physiologic dosages of cortisone acetate and hydrocortisone, interesting potential uses were encountered that were either new or had been forgotten. I continued to present at meetings and publish results of our work, and following each presentation a number of interested inquiries were received, but nothing more happened. In retrospect, it appears that the failure of pharmaceutical houses to follow up promotionally in the manner that physicians

are accustomed to expecting when improvements in therapy are reported caused interested physicians to decide that the therapy must not have been as effective as my reports implied. There have, however, been no reports indicating that any results I have published could not be substantiated.

As time passed, the attitudes of grant committees and editorial boards changed. Requests for funds to study these new uses were denied, and reports of the promising potential of the safe dosages were turned down for publication. It became evident that cortisone and hydrocortisone had achieved such a bad reputation that many members of these committees or boards hesitated to accept or publish any report that suggested they might have further potential benefit.

In the course of my researches, I was in touch with Fuller Albright until his death and also with Dwight Ingle, the distinguished physiologist at the University of Chicago School of Medicine. Both offered encouragement. I saw Dwight each year at the Laurentian Hormone Conference, where we had lively discussions of our mutual interests in adrenal physiology. He had a continuing interest in my observations on patients and encouraged my attempts to have these published. Unfortunately, he died of a heart attack on July 28, 1978.

Many of the investigators who participated in the first clinical studies with these steroids have retired or died, and younger investigators have been so strongly indoctrinated with the hazards of glucocorticoids that they seem to be unaware of the safety of physiologic dosages, so I decided to review the cortisone story in an attempt to restore perspective and to present my observations with the hope of stimulating others to return to the study of the *physiologic* effects of hydrocortisone and its proper place in clinical medicine.

One of the aspects of this type of therapy that has strained its credibility is the wide variety of pathologic disorders that are benefited. It is difficult to believe that one therapeutic agent could help so many conditions. Yet, recent findings regarding the etiologic role of autoimmunity in many diseases whose cause was unknown provide an explanation of some of these previously unexplained beneficial effects, since, for reasons that are not clear, glucocorticoids are known to benefit autoimmune disorders. In fact, the mechanism of any of the beneficial effects of glucocorticoids is not known. Speculations regarding recent studies in this area provide further reasons for encouraging continuing investiga-

tions in this field. Evidence that physiologic dosages of cortisone or hydrocortisone may improve resistance to viral infections, in contrast to the known harmful effects of pharmacologic dosages that decrease such resistance, opens another area warranting careful study.

Many of the promising clinical uses described in this book require further investigation to determine the proper scope of such uses, and additional experience is advisable to confirm the safety of this therapy in the hands of others, but in over one thousand patient years of experience with the dosages described, none of the harmful potential of larger, *pharmacologic* dosages has been encountered. It would have been easier to relax and forget the cortisone problem, but the therapeutic promise of this type of treatment is too great.

In writing this book, no attempt has been made to refer to the entire literature regarding the various subjects discussed—it is much too vast—but an attempt has been made to cite pertinent reports; from these the interested reader may obtain a more complete bibliography on a particular subject. Much of the book consists of case reports because these represent experiments of nature, and careful observations often provide evidence of clinical efficacy and clues to further advances in knowledge in a manner that is not possible in statistical analyses or double-blind placebo studies.

If this book stimulates researchers and clinicians to reevaluate their fears about the hazards of cortisone therapy and causes them to consider further possible beneficial effects of physiologic dosages, its purpose will have been achieved.

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I am indebted to the University of Virginia School of Medicine, from which I graduated in 1940, for appointing me a Clinical Professor of Internal Medicine after my retirement from Case Western Reserve University, thereby enabling me to continue research and writing about the increasingly promising potential of the use of safe, physiologic dosages of cortisol in clinical medicine, to my son, Dick, for teaching me to use my Macintosh LCII in order to compose the manuscript for this second edition, and to my daughter, Leslie, for reviewing and preparing the manuscript for mailing to the publisher and for preparing the index for the book.

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CONTENTS

SAFE USES OF CORTISOL

Chapter 1

BACKGROUND

In 1949, when Dr. Philip Hench and his associates at Mayo Clinic reported the remarkable effects of cortisone and adrenocorticotropic hormone (ACTH) on patients with rheumatoid arthritis,[1] their discovery was greeted as a major advance in the field of medicine. The Nobel Prize awarded for this work reflected the significance that was attached to it. Not only were patients previously crippled with arthritis helped to get back on their feet and become active members of society again, but patients with other so-called "collagen diseases" such as disseminated lupus erythematosus, polyarteritis nodosa, and scleroderma were dramatically benefited; patients with allergies such as bronchial asthma, hay fever, and eczema received impressive relief; patients with some types of leukemia and other malignancies went into temporary remissions; and those with numerous other disorders experienced unprecedented improvement from these agents. It is not surprising that cortisone came to be known as the "miracle medicine." Yet, within a few years, cortisone fell into such disfavor that it was considered a dangerous drug whose use should be reserved for serious illnesses when no other treatment was effective. That it is a normal hormone was largely forgotten, and that many patients take it for years with no harmful side effects was generally overlooked. Actually, many patients cannot live normal lives without it, and while taking it they are as normal as any healthy person. Furthermore, there are other potential uses of this medication in safe dosages that appear even more promising than the known uses of the hazardous dosages. There is even convincing evidence that it can improve resistance to the common cold and influenza!

How could such a situation occur? What is the evidence that cortisone can be safe? In what other conditions does it show therapeutic potential? Why is it still one of the most promising therapeutic agents of all time? As an initial step in attempting to answer these questions, the history of

the cortisone story will be briefly reviewed and an effort made to restore perspective.

HISTORY

In 1929, Dr. Hench saw a patient whose rheumatoid arthritis had "disappeared" within a week after the sudden development of jaundice.[2] Later he noted that pregnancy often resulted in impressive improvement of arthritis, followed by a relapse after delivery.[3] Subsequently, temporary improvement in rheumatoid arthritis was noted when patients underwent such varied clinical conditions as surgical procedures, general anesthesia without surgery, therapy with ergosterol, estrogens, or testosterone, a high fat (ketogenic) diet, or starvation.[4] After much speculation and clinical investigation, he decided that the agent responsible for improvement under these numerous apparently unrelated circumstances might be a normal adrenocortical hormone.

In 1930, Dr. Edward C. Kendall had undertaken a chemical and physiologic investigation of the adrenal cortex in the biochemical laboratories of the Mayo Foundation for Medical Education and Research.[5] In 1934, the first crystalline compounds were separated and designated "Compounds A, B, C, and D." In the following year, Compounds E and F were isolated, and chemical formulas were assigned to these compounds in 1937 and 1938. Dr. Dwight Ingle, who was working in Dr. Kendall's laboratory, demonstrated that Compound E had a beneficial effect on muscular work capacity in rats.[6] Later, this compound was found to influence carbohydrate metabolism, and other investigators showed that it increased physiologic resistance to stress or cold and to toxic substances such as typhoid vaccine.[7]

By 1940, it had become evident that investigation of the effects of Compounds A, B, E, and F in human subjects was desirable, but no method of obtaining sufficient supplies for clinical studies was known. In the fall of 1941, just before Pearl Harbor, requests were made to the National Research Council by the medical departments of the Army and Navy for a large supply of the hormones of the adrenal cortex, because it was believed that they might be of value in the event of military conflict. Interest in these hormones was heightened by a rumor that pilots of the German Luftwaffe were injected with adrenal cortical extract and that this enabled them to fly with ease at altitudes of 40,000 feet or

more.[5] During the war, twenty-two laboratories in the United States were attempting to prepare hormones of the adrenal cortex, but by 1945, after interest in potential military use of adrenocortical hormones had subsided, only the laboratories of the Mayo Foundation and of Merck & Co., Inc. persisted in this search.

The combined efforts of these two laboratories resulted in the production of a sufficient quantity of Compound E to initiate limited clinical studies in the spring of 1948. Dr. Randall Sprague and his associates received a small quantity for treatment of three patients with adrenal insufficiency at the Mayo Clinic, and they tried dosages of 50 and 100 mg intramuscularly daily with beneficial effects.[8] In September, 1948, when Hench and his group received a supply of Compound E for clinical investigations in arthritics, the larger dosage of 100 mg daily was decided upon.[1] In retrospect, this was a fortuitous decision because, with the preparation and schedule of administration they used, a smaller dosage might not have produced impressive clinical benefit.

The first arthritic patient to be given Compound E was a twenty-nine year old woman with severe rheumatoid arthritis of four and one-half years duration who had received many treatments without significant improvement. On September 21, 1948, she received her first injection of 50 mg of Compound E intramuscularly, and this was continued twice daily. The following day little evidence of improvement was apparent, but when she awoke on September 23 she noted much less muscular soreness. On September 24, painful morning stiffness was entirely gone, and whereas she had scarcely been able to walk three days previously, she now walked with only a slight limp. By the seventh day of treatment, "articular as well as muscular stiffness had almost completely disappeared, and tenderness, pain on motion, and even swellings, had markedly lessened." [1]

Over the next six months, a total of fourteen patients with severe or moderately severe rheumatoid arthritis were treated. Between September, 1948, and January, 1949, Compound E was used, but it was then found that the less expensive and more easily prepared Compound E acetate "was absorbed with sufficient promptness," so subsequently patients received this preparation. An interesting comment was that "early preparations used for our first three patients were potent and devoid of side effects," but then difficulties were encountered. When two subsequent preparations were substituted in patients who had previ-