Third Edition

SAFE USES OF CORTISOL

WILLIAM McK. JEFFERIES

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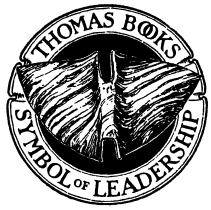
By

WILLIAM McK. JEFFERIES, M.D., F.A.C.P.

Retired Clinical Professor of Internal Medicine
University of Virginia School of Medicine
Charlottesville, Virginia
Formerly Assistant Clinical Professor of Medicine
Case Western Reserve University School of Medicine
Cleveland, Ohio
Former Consultant in Endocrinology
Euclid Clinic
Lutheran Medical Center
St. Vincent Charity Hospital
University Hospitals of Cleveland



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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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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-

ously been benefited by injections of Compound E, articular flare-ups promptly occurred, and sedimentation rates rose quickly. It was noted that in earlier preparations, crystals were fairly large, possibly slowing absorption and providing a longer sustained effect, whereas later preparations contained smaller crystals, were easier to administer and more rapidly absorbed.

Because larger doses of the new preparations seemed necessary to produce rapid clinical improvement, and because 100 mg of Compound E acetate was the chemical equivalent of 89 mg of Compound E, Hench and his group were inclined to attribute the requirement for larger doses to the change to the E acetate. They accordingly began to administer 300 mg Compound E acetate on the first day, followed by 100 mg daily thereafter,[9,10] still on a schedule of one or two intramuscular injections daily.

In retrospect, it seems likely that some of the difference in therapeutic effectiveness could have been related to the difference in crystal size, the larger, more slowly absorbed crystals providing a greater antiarthritic effect than the smaller, more rapidly absorbed ones, especially with the schedule of administration of only once or twice daily that was used. At the time, however, this possibility was apparently not considered.

After patients obtained initial optimum improvement, generally within seven to fourteen days, their daily dosage was reduced to 75, 50, or even 25 mg, with the hope of finding a smaller, more economical, effective maintenance level. Unfortunately, flare-ups occurred and sedimentation rates rose promptly in most cases treated in this manner. They therefore concluded that "so far a minimum daily dosage of 75 mg to 100 mg seems required and sometimes such a dose does not entirely control symptoms and sedimentation rates." They mentioned cushingoid changes in only one of their patients, the first whom they treated and the one who seemed to be particularly resistant to treatment, requiring repeated administration of larger doses. Later, signs of hypercortisolism began to appear in other patients, so Compound E acetate therapy was interrupted, with intervals of several days to weeks between courses. They stated,

> . . . we observed no notable reactions of toxicity when later preparations of Compound E or E acetate were used. Transient epigastric pain occurred occasionally but was relieved with cessation of dosage for a few days. Transient edema, generally pretibial, occurred occasionally, but it disappeared, sometimes spontaneously, or when the dosage was reduced.[10]

The term "cortisone" was not introduced until several months after the initial report.[9] Because corticosterone, Kendall's Compound B, was one of the first adrenocortical steroids to be identified, other adrenocortical steroids were often termed as chemical relatives of this steroid. Hence, Compound E was also known as 11-dehydro-17-hydroxy-corticosterone. The term cortisone was introduced as a simplification of the unwieldy chemical name for practicing physicians and the general public. Later, when Kendall's Compound F was found to be equally effective in the treatment of arthritis, it came to be called "hydrocortisone" because it differed from cortisone only in the presence of a hydroxyl group instead of a ketone group on the eleventh carbon atom. Subsequently, chemists recommended that hydrocortisone be termed cortisol because the suffix -one referred to a ketone grouping, such as was present in cortisone, but the proper suffix for a hydroxyl group was -ol. Unfortunately, the spoken words cortisol and cortisone sound so similar that they may be confused, so many clinicians have continued to refer to Compound F as hydrocortisone, except when referring to its level in the blood, when the term "plasma cortisol" is more commonly used. Because cortisol is the chief glucocorticoid produced normally by the human adrenal cortex, cortisone being converted to it prior to the production of effects in the tissues, it is more frequently used for physiologic effects today. As the years have passed, medical students and practicing physicians have become more familiar with the term "cortisol," so it will be used in this second edition to refer to hydrocortisone or Kendall's Compound F.

In retrospect, besides the interrupted courses, there are other possible explanations of why so few side effects were observed in these initial studies. It is now known that under normal, unstressed conditions the adrenals produce the equivalent of 35 to 40 mg of cortisone acetate taken by mouth in divided doses daily,[11] so the initial dosages used by Hench and his group were considerably in excess of this normal production and, hence, would be expected to produce the characteristic effects of hypercortisolism. Because these dosages were administered intramuscularly in preparations that were relatively rapidly absorbed, however, and in only one or two injections daily, and since it has been demonstrated that the same total daily dosage of cortisol taken in four divided doses before meals and at bedtime is more effective than when taken in two divided doses at twelve-hour intervals,[12] the schedule of the early injections would be less effective and less likely to produce

side effects than the same total dosage being administered at more frequent intervals throughout the twenty-four hours.

Hence, if the first preparation used by Hench had been the type of cortisone acetate that is available today, and if it had been administered in divided dosages as it is today, a daily dosage of 100 mg would probably have produced more side effects more quickly, and smaller dosages might have been clinically effective. *It should, therefore, be borne in mind that conclusions regarding dosages necessary for clinical effects based upon the observations of the earlier investigators may not be valid when applied to later preparations and schedules of therapy.*

In addition, it is now known that smaller dosages of cortisone or cortisol may take ten to fourteen days to produce impressive improvement in arthritis so that possible beneficial effects of smaller dosages used as initial therapy might have been missed because they were not continued for a sufficient period of time, even if they had been administered on an optimum schedule.

After it was found that cortisone acetate and cortisol were effective by mouth[13,14] when the daily dosage was divided into several portions, beneficial effects in numerous diseases were reported. These were summarized in an excellent review by Thorn and his associates.[15] Unfortunately, reports of undesirable side effects also began to multiply. These included rounded or "moon face," thinning of the skin with easy bruisability and appearance of striae, subcutaneous hemorrhages, osteoporosis, spontaneous fractures, and fluid retention with edema. Peptic ulcers were also attributed to cortisone or cortisol therapy, but the concomitant use of salicylates was probably a significant factor in their production. Initial dosages were, therefore, reduced to 100 mg daily and maintenance dosages to 50 mg daily, and the undesirable side effects did not appear quite so quickly, but they still occurred. Later, two even more alarming side effects became evident. Patients on cortisone therapy demonstrated a diminished resistance to infection, and if they underwent even minor surgical procedures, they might collapse and die under the anesthetic.

Such complications understandably caused alarm and consternation on the part of the medical profession and the public. A therapeutic agent that had been welcomed as a miraculous advance had been found to be potentially a treacherous poison. Derivatives of cortisone and cortisol that had greater anti-inflammatory and less sodium-retaining effects,

such as prednisone, prednisolone, triamcinolone, methyl prednisolone, and dexamethasone, were introduced with the hope that they would be safer, but the only side effect that was reduced was the sodium-retaining effect, and the other hazardous potentials remained. This group of steroids, which had in common the property of stimulating the conversion of protein to carbohydrate (gluconeogenesis), came to be termed glucocorticoids.

Reports of additional serious and sometimes devastating complications of glucocorticoid therapy began to multiply; ophthalmologists reported development of cataracts and aggravation of glaucoma; internists and general practitioners reported osteoporosis with pathologic fractures, development of peptic ulcers with occasional perforation, lowering of resistance to infection, development of diabetes mellitus, and appearance of serious psychological disorders and even psychoses. Surgeons reported possible interference with wound healing as well as collapse and death after general anesthetic for relatively minor surgery.

Not every patient treated with glucocorticoids developed such alarming complications, but some did, and practically every practitioner encountered one or more serious complications of this type. It is not surprising that the attitude of physicians toward glucocorticoid therapy reversed from enthusiasm to alarm and that reports advocating reservation of the therapeutic use of these agents for serious, life-threatening diseases for which no other therapy was effective replaced the widespread enthusiastic use for many diseases that had previously been prevalent. Medical literature was swamped with reports of grim complications of glucocorticoid therapy, optimism gave way to pessimism, and a situation gradually developed in which perspective was lost.

Any dosage of any glucocorticoid was considered potentially hazardous. Reports of undesirable effects often failed to state the dosage and duration of administration, implying that all dosages were capable of producing similar effects. The term "cortisone therapy" was applied indiscriminately to treatment with other glucocorticoids, making it difficult to evaluate differences between glucocorticoid preparations or even to determine what steroid a patient had received. The literature abounded with statements that all glucocorticoid therapy is dangerous, hence it should not be started except as a last resort and should be discontinued as soon as possible. For over thirty years physicians have been indoctrinated with this concept.

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Chapter 2

SOURCES OF CONFUSION

That cortisone and cortisol are normal hormones of the adrenal cortex implies that in physiologic dosages they must be safe. This implication is confirmed by the clinical experience of patients with adrenal insufficiency or congenital adrenal hyperplasia. When given suitable maintenance dosages, they can take cortisone or cortisol indefinitely without undesirable side effects and enjoy perfectly normal health. Other patients in our clinics have received small, physiologic dosages of cortisone or cortisol for various conditions that will be described later, totaling *over one thousand patient years of experience.* Other than an occasional incidence of acid indigestion, usually resulting from taking the steroid on an empty stomach, or a rare instance of a patient being allergic to an ingredient of the filler in the steroid tablet, no undesirable side effects whatsoever have occurred.

It is not generally realized that the dangerous side effects of glucocorticoid therapy occur only with certain dosages and not with others. That there is a tremendous difference between the effects of small "physiologic" dosages and those of larger "pharmacologic" dosages has not been emphasized.

For example, it is widely recognized that glucocorticoids, including cortisone and cortisol, produce a negative nitrogen balance, but this is not a normal physiologic effect. If it were, all hypoadrenal patients on replacement therapy would be in negative nitrogen balance, but they obviously are not. Ingle and Baker,[1] in 1953, emphasized that cortisone and cortisol inhibit anabolism only when administered in excess, but this fact apparently received little attention. The few metabolic balance studies that have been performed on patients with adrenal insufficiency clearly demonstrate that physiologic replacement dosages do not cause nitrogen loss.[2,3] Recent studies in rats have shown that corticosterone administration does not cause protein loss and cessation of growth until dosages sufficient to raise plasma levels of steroid above the normal

range are administered.[4] The concept that a negative nitrogen balance is a normal physiologic effect of cortisone or cortisol is therefore as erroneous as one that hypoglycemia is a normal physiologic effect of insulin.

When applied to hormone actions, a "physiologic" dosage implies one that promotes normal function, whereas a "pharmacologic" dosage is one in excess of normal requirements and, hence, one that might alter normal function. To determine the normal physiologic effects of any hormone, it must be administered to subjects deficient in this hormone and in no other and in a dosage comparable to the level of production of this hormone in normal subjects. Unfortunately, few studies of the effects of cortisone or cortisol have been made under such circumstances.

Because the beneficial therapeutic effects in rheumatoid arthritis and other diseases were obtained with dosages of 50–150 mg daily, metabolic balance studies and other clinical investigations of their effects employed comparable dosages.[2,5–20] It is not surprising, therefore, that physicians became familiar with the pharmacologic, rather than the physiologic, effects of these steroids. In a few studies,[2,3,7] dosages of cortisone acetate of 50 mg or less per day were administered to patients with adrenal insufficiency, but these observations were either incidental to studies of effects of other steroids or the manner of administration was different from that employed clinically today.

All other studies of the metabolic effects of these steroids have involved the administration of dosages in excess of normal requirements and in most cases to subjects who have not had demonstrated adrenal insufficiency. The well-known effects of glucocorticoids are, therefore, not their normal physiologic ones but those resulting from administering excessive dosages to subjects, many of whom may not have needed them. These "pharmacologic" effects include excessive sodium and fluid retention, potassium depletion, nitrogen and calcium loss, and elevation of blood sugar.

The failure to differentiate between physiologic and pharmacologic effects has been a major factor in the confusion regarding the clinical value of these agents. When it was found that a normal replacement dosage for an adrenalectomized patient was 35–40 mg of cortisol daily, it became evident that dosages above this level were in excess of physiologic requirements, but by this time such serious side effects of the larger dosages had been reported that cortisone and cortisol had achieved a

reputation of being dangerous drugs. The possibility that smaller dosages might be safe was not considered, and patients receiving any dosage were through to be in jeopardy.

With cortisone or cortisol, as with any normal hormone, there are three dosage ranges that can be administered:

1. **Replacement dosage.** In the case of cortisol, this is a dosage equal to that which, in association with physiologic amounts of sodium-retaining and androgenic steroids, is necessary to maintain a totally adrenalectomized patient in normal health in the unstressed state. Physiologic studies indicate that the average daily production of cortisol by human adrenals under basal conditions is approximately 15–20 mg, but this dosage will not maintain a totally adrenalectomized patient. Studies with cortisone acetate in four doses daily (with meals and at bedtime) indicate that approximately 35–40 mg daily is necessary to inhibit endogenous adrenal steroid production to zero,[21] and this dosage will satisfactorily maintain an adrenalectomized patient with a minimum of supplementary sodium-retaining steroid. Hence, this may be considered a *replacement dosage.* Although cortisol is slightly more potent than cortisone acetate, a replacement dosage of cortisol is approximately the same, 35–40 mg daily. Because cortisone must be converted to cortisol before being clinically effective, it is no longer recommended for replacement therapy. The discrepancy between the 20 mg average daily production by normal adrenals and the 35–40 mg necessary to suppress normal adrenocortical activity implies that, when taken by mouth in tablet form, even in divided doses, cortisone acetate or cortisol is only approximately 60 percent as efficient as when the hormone is naturally produced by the adrenals and released directly into the blood in accordance with bodily needs.

If a replacement dosage is given to a patient with intact adrenals, it will, therefore, suppress his or her adrenal function completely, but because the ultimate effect is a level of glucocorticoid not in excess of normal requirements, the effects of hypercortisolism will not develop. If the suppression of endogenous adrenal function persists sufficiently long, the adrenals may not be able to respond adequately to stress, and the patient may experience temporary adrenal insufficiency after glucocorticoid therapy is withdrawn.

2. **Suprareplacement dosages.** These are in excess of normal physiologic requirements. In the case of cortisone or cortisol, these would be

dosages larger than 40 mg daily. These are the dosages implied in most clinical literature, and if continued for a sufficient period of time, they can produce all of the undesirable side effects of hypercortisolism.

3. **Subreplacement dosages.** These are dosages less than normal replacement dosages and, hence, are capable of suppressing endogenous adrenal function only partly. It has been demonstrated that when subjects with intact adrenals receive less than full replacement dosages of cortisone acetate or cortisol, endogenous adrenal function is suppressed only sufficiently to achieve a normal total glucocorticoid level.[21] For example, subjects receiving 20 mg (5 mg four times) daily of cortisone acetate have their endogenous adrenal steroid production decreased by approximately 60 percent, and subjects receiving 10 mg (2.5 mg four times) daily have their adrenal steroid production decreased by approximately 30 percent (Fig. 1). The residual functioning tissue is adequate for apparently normal responses to stresses such as respiratory or gastrointestinal infections or even major surgery,[21] but because of the possibility that their reserve capacity to cope with stress or that their hypothalamus-pituitary-adrenal (HPA) response to stress might be impaired, and because of recent evidence that at least some autoimmune disorders are associated with a defective HPA response to stress (see Chapter 6), it is seems advisable to supplement their cortisol dosage at times of any increased stress and especially at times of surgery or similar severe stress as in patients with more severe adrenocortical deficiency. Barker[22] has reported that adrenal insufficiency in the unstressed state does not occur unless 90 percent or more of the cortical tissue is destroyed, but the demands of varying degrees of stress upon the adrenals' ability to respond have apparently not been studied, nor have the long-term effects of stress, either acute or chronic, upon patients with lesser degrees of adrenal deficiency been investigated. It is therefore considered advisable to give patients taking subreplacement dosages of cortisone or cortisol the same printed instructions as those taking full replacement dosages (see p. 20). Subreplacement dosages also avoid the complete suppression of endogenous adrenal androgen production that probably causes a higher incidence in women than in men of undesirable side effects such as osteoporosis when larger dosages are taken for long periods. Many patients who need subreplacement dosages have low adrenal reserve, so the administration of such dosages actually improves the adrenals' ability to respond to stress in these cases.

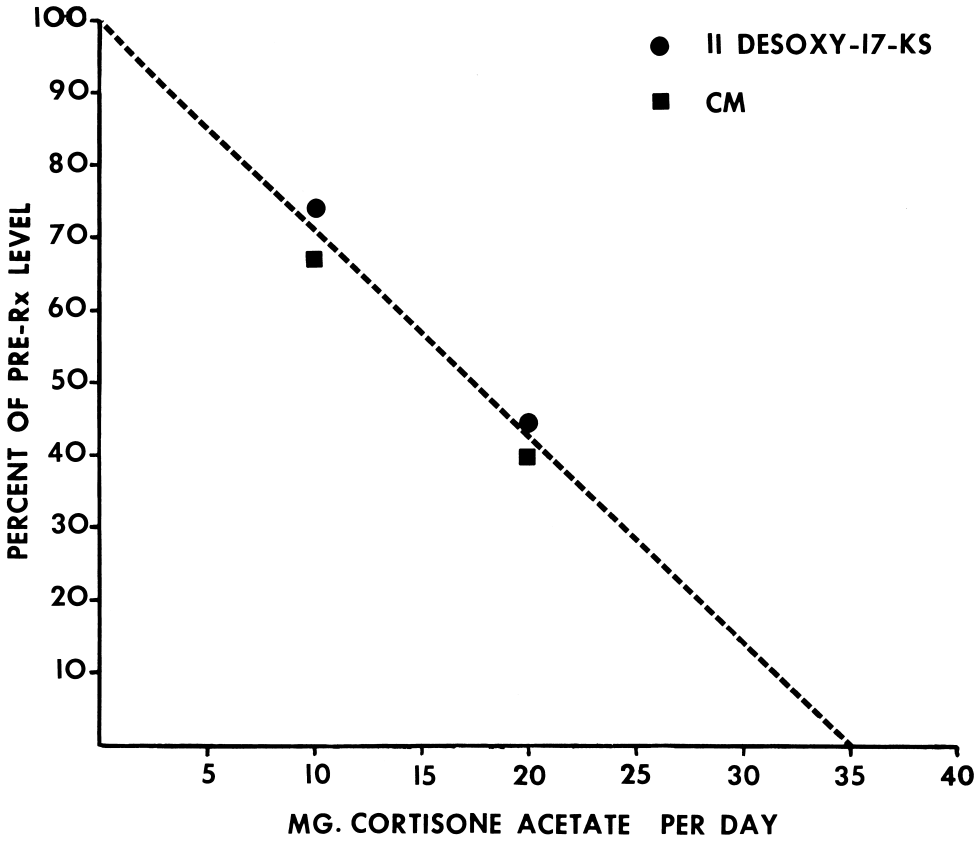

Figure 1. Effects of low dosages of cortisone acetate taken as 2.5 or 5 mg four times daily upon urinary excretion of 11-desoxy-17KS and cortisol metabolites (CM) from endogenous sources. From William McK Jefferies, Low Dosage Glucocorticoid Therapy, *Archives of Internal Medicine, 119:*265–278. Copyright 1967, the American Medical Association. Reprinted by permission.

The schedule of administering cortisone acetate or cortisol every eight hours or four times daily is followed because of evidence that normal blood levels and some metabolic effects of a single dose of cortisol do not last longer than eight hours.[23] For practical purposes, dividing the total daily dosage into four parts taken before each meal and at bedtime has two advantages. It is easier for a patient to remember to take a medication at these times than at other times, hence this schedule provides a convenient way of spreading out the day's dosage, and the ingestion of food tends to counteract the development of acid indigestion from the stimulation of gastric acid and pepsin that may be produced by the

steroid. For the bedtime dose, patients are instructed to drink milk or take an antacid with the medication.

The schedule on which the daily dosage is taken is apparently important not only in the achievement of clinical benefit but also in the avoidance of undesirable side effects. In our studies, administration of cortisone acetate or of cortisol in subreplacement dosages of 5 mg every 8 hours or four times daily produced no elevation of plasma 17-hydroxycorticosteroids (17-OHST), nor of excretion of urinary 17-OHST, nor any metabolic changes characteristic of glucocorticoid excess[21] (Fig. 2).

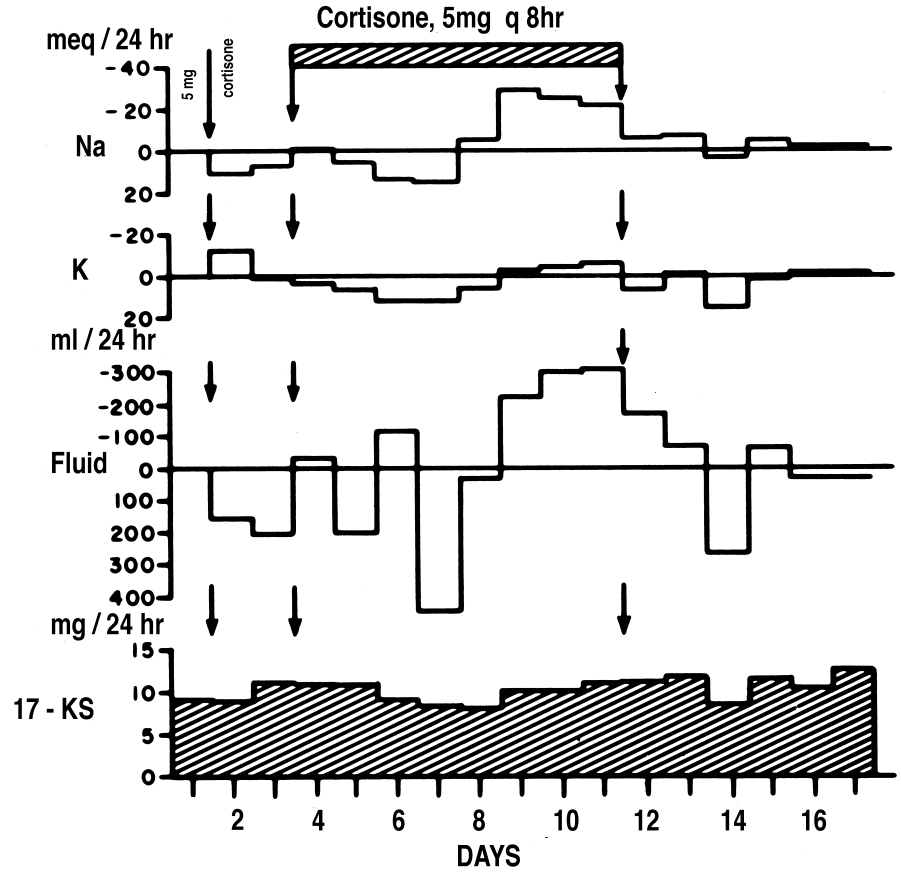

Figure 2. Effects of administration of a single dose of 5 mg of cortisone acetate and of 5 mg every 8 hours for 8 days upon urinary sodium, potassium, fluid, and total neutral 17-ketosteroid (17-KS) excretion. From William McK Jefferies, Low Dosage Glucocorticoid Therapy, *Archives of Internal Medicine, 119:*265–278. Copyright 1967, the American Medical Association. Reprinted by permission.

After the initiation of cortisone or cortisol therapy at these dosages, up to ten days are required before a new stable state is reached, so this may be related to the observation that therapeutic effects may not appear until 10–14 days after treatment is started.

Shuster and William[24] have reported that a single dose of cortisone acetate as small as 12.5 mg daily administered to normal subjects caused increased excretion of 17-OHST. Their data indicate that urine collections for 17-OHST were made on the third day of administration. The discrepancy between their observations and those in our studies might, therefore, be due to two factors: (1) With the evidence that the pituitary-adrenal mechanism requires longer than three days to adjust to the administration of small doses, some degree of summation effect might be expected on the third day. (2) Because Nelson and his associates found that a single oral dose of 12.5 mg of cortisone acetate may cause a transient rise in plasma 17-OHST,[25] this might result in a greater increase in urinary steroid excretion than the same amount administered in divided doses. These investigators also reported that patients receiving 12.5 mg cortisone acetate twice daily had normal basal plasma 17-OHST levels, indicating that such dosages did not produce a persistent elevation of plasma cortisol. They further reported that a single oral dose of 12.5 mg of cortisol caused a peak rise in plasma 17-OHST in one hour with a return to the baseline level by the fourth hour, but the effects of persistent administration of this dosage were not studied. Barbato and Landau[26] reported that 25 mg cortisone acetate or cortisol taken orally produced a peak value of serum cortisol in one to three hours, and by the fifth hour at least one subject had low serum cortisol. A single daily dose of 20 mg of cortisone acetate or cortisol might, therefore, have a different effect on the hypothalamic-pituitary mechanism from the same total amount administered in divided doses throughout the twenty-four-hour period. For this reason, the administration of a single dose of 0.5 mg of dexamethasone[27] or 5 mg of prednisolone[28] in the evening, even though apparently effective in inhibiting adrenocorticotropic hormone and in producing anti-inflammatory effects, is less physiologic than the low dosage cortisone or cortisol schedule used in our studies. These doses of dexamethasone and prednisolone, being equivalent to approximately 15 mg and 20 mg of cortisol, respectively, represent individual doses three or four times as great as the 5 mg used in our clinic. Their action is probably more similar to that of larger doses administered every

other day[29] wherein an intermittent excess of steroid is achieved. Furthermore, the duration of effects of a single dose of the steroid derivatives is longer than that of cortisol, so observations made with natural steroids may not be applicable to derivatives or vice versa.

It is evident from the above that either full replacement or suprareplacement dosages of cortisol may be hazardous if given for a sufficient period of time, but subreplacement dosages on a divided schedule do not possess such harmful potential.

Why should most physicians be unaware of the safety of the small physiologic dosages? Three major reasons for this are as follows:

1. There has been no promotion of physiologic dosages by pharmaceutical companies. Patents on cortisone and cortisol have expired, and drug regulations require that when a new use is found for an old drug, even at a lower dosage, it must be treated as if it were a new drug and meet all of the investigational requirements of a new drug before the use can be included in the package insert or advertised. Although this requirement is obviously desirable, there is little incentive for a pharmaceutical company to invest the sums necessary to meet these requirements when any competitor could market the drug, especially in the case of medications such as cortisone and cortisol, where such a great apprehension exists that a major educational program would be necessary to have the product accepted.
2. There has been little, if any, discrimination between the effects of physiologic versus pharmacologic dosages. Package inserts for cortisol and cortisone acetate, for example, do not differentiate between physiologic and pharmacologic dosages and effects, implying that any dosage may cause any of the numerous grim side effects that are included in the sections on warnings, precautions, and adverse reactions! This not only causes physicians to be unaware of the safety and proper usage of physiologic dosages, but with the recent emphasis upon package inserts being made available to patients, has caused patients with conditions that require physiologic dosages in order to be able to live normal lives, such as adrenal insufficiency or congenital adrenal hyperplasia, to become so frightened that much reassurance is necessary to convince them that this lifesaving medication is not going to poison them! Thorn described this problem as

long ago as 1966,[30] and subsequently it has, if anything, become worse.

3. There is a tendency to confuse cortisone and cortisol with their more potent derivatives, such as prednisone, prednisolone, methyl prednisolone, triamcinolone, and dexamethasone. As noted above, with the profusion of glucocorticoid agents there has been a tendency to term all glucocorticoid therapy "cortisone therapy" regardless of the steroid used. A dosage of 5 mg four times daily of cortisone acetate or cortisol is a safe, physiologic dosage, but 5 mg four times daily of prednisone or any of the other derivatives is at least four times as potent and, hence, subject to all of the hazards of pharmacologic dosages. These and other factors that have contributed to the confusion regarding the safety of glucocorticoid therapy have been reviewed elsewhere.[31–33]

Perhaps another factor that has contributed to the failure to recognize the value and safety of low dosage glucocorticoid therapy is the inconvenience of having patients take three or four doses daily for optimum effects. This requires more time in the physician's office for explanation of the schedule and more difficulty on the part of patients in following it. Most patients are willing to accept this inconvenience if the reason is explained, especially after they have had an opportunity to experience its beneficial effect. Verbal instructions are often forgotten, so we routinely give printed instructions, an example of which is reproduced on the next page, to every patient starting on glucocorticoid therapy. This is reinforced by a discussion in which the patient is encouraged to ask questions. Understanding and cooperation of the patient are essential for this type of therapy and cannot be overemphasized.

Patients with more severe degrees of adrenal deficiency will probably be treated by endocrinologists and given prescriptions for parenteral cortisol (Solu-Cortef®) and sterile syringes and needles with instructions for their use.

INSTRUCTIONS FOR PATIENTS TAKING CORTISOL

Please read carefully and keep in a place they can be referred to frequently, such as a bulletin board or refrigerator door.

The medication that has been prescribed for you is a normal adrenal hormone. In the dosage that has been prescribed, it will not cause any of the harmful side-effects that can result from an excessive dosage, but the instructions must be followed carefully. For this reason, the medication should be kept out of the reach of children or others who might take it by mistake. You will notice that the tablets taste somewhat bitter; so, like aspirin, if they are taken on an empty stomach they may cause gastric discomfort and indigestion. It is helpful, therefore, to take them just before meals or with milk or an antacid. If you have ever had a peptic ulcer (of the stomach or duodenum), you should always take an antacid with each dose.

The medication is more effective if you spread out the day's dosage, so you should take _____ tablet with each meal and at bedtime (or _____ tablet with breakfast, _____ tablet with lunch, _____ tablet with supper, and _____ tablet at bedtime), totaling _____ tablets daily. It may be taken before, during, or after meals, but most patients prefer to take it just before meals. If a meal will be delayed over 2 hours or missed, try to take the medication at the usual mealtime. If you forget to take a dose, for example at lunchtime, and remember it in the afternoon, take it when you think of it. If you do not remember it until the next dose is due, take both doses at the same time in order to have the correct total dosage for the day. It will not be harmful to double up on doses, but the medication will be more effective if you take each dose at the proper time. It is helpful to have a small pillbox in which each day's dosage is placed each morning and which is carried with you in your pocket or handbag at all times. This not only reminds you to take the medication, but also enables you to determine whether you have taken a dose. Sometimes it is difficult to remember whether you have taken a dose.

If you go on a vacation or trip, take at least two complete supplies of medication packed separately. Carry one with you and pack the other in your luggage. Then if one is lost, the other supply can replace it, because it might be difficult or expensive to replace medication when you are away from home. If you have mild or more severe adrenal deficiency, you should wear a Medic-Alert bracelet at all times in case you are in an accident and knocked unconscious, because doctors treating you need to know this in order to provide optimum treatment. If you do not have one, ask my secretary or me how to order one.

Because this is a normal hormone, it will not interfere with your taking any other medication. If you should develop symptoms of an incipient respiratory infection, such as a sore throat or nasal congestion, take a double dose of cortisol immediately and continue the double dosage until you have felt completely well for at least 24 hours, then return to your basic dosage. If symptoms last longer than a week, phone me. If you should develop symptoms of incipient influenza (chills, fever, malaise, aching), take 20 mg immediately and continue 20 mg four times daily until you contact me by phone. You should also take any other medication prescribed by me. If you develop "intestinal flu" (nausea, vomiting, diarrhea), take a double dosage of cortisol as soon as you can hold it down and phone me.

When these instructions are followed, infections usually clear more quickly, provided you do not smoke. If you smoke, you should stop smoking during any illness, as smoking will tend to delay your recovery and possibly cause complications. If any other questions arise, phone me.

(Name)
(Office Address)
(Office Phone Number)

The investigation of low dosage glucocorticoid therapy has also been handicapped by an attitude on the part of some authorities that everything is known about the clinical effects of cortisone and cortisol, so there is no reason to spend more time and effort studying them further. Such an attitude is not valid because, although much is known about the harmful effects of large doses of glucocorticoids, very little is known about the mechanism of any of their beneficial clinical actions. Recent studies of the hypothalamus-pituitary-adrenal (HPA) axis have confirmed the importance of normal adrenocortical function in response to infection and other stresses, so this situation is improving. It is discussed in Chapters 6 through 9.

Finally, the possibility of undesirable effects of long-term administration of low doses must be considered. There are several reasons why this is unlikely. First, the uses for which they are given are directed towards restoring normal function rather than altering normal function. Second, the dosages do not produce any excessive steroid level in the blood. Third, although such dosages may affect diurnal variation in plasma cortisol levels, they do not destroy this normal diurnal variation (Fig. 3).

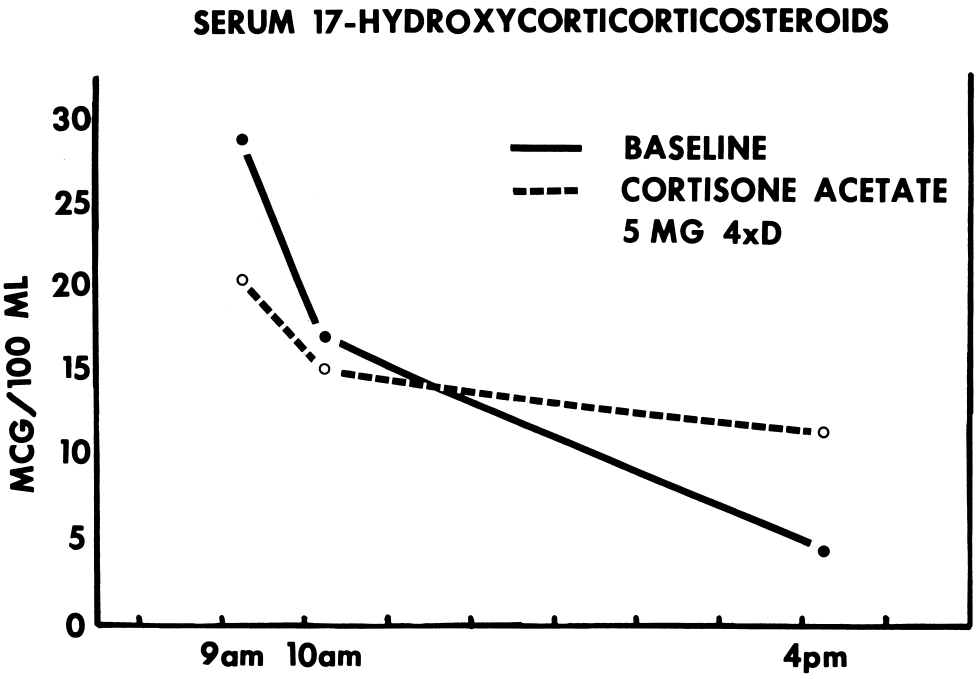

Figure 3. Effects of 5 mg cortisone acetate four times daily for 14 days upon diurnal variation of serum 17-hydroxy-corticosteroid levels in a normal male.

Fourth, patients who have been taking subreplacement dosages for long periods respond to ACTH and metyropone comparably to normal subjects.[21] Fifth, there is no evidence that patients who have taken physiologic dosages for over forty years have experienced any harmful effects, nor that children born to women taking physiologic dosages have any increased incidence of congenital defects or other difficulties.

The result of this combination of factors is a unique situation in which a safe therapeutic regimen with promising potential in several broad clinical areas has been practically ignored. A review of the known therapeutic effects of physiologic dosages plus suggestive evidence for even greater therapeutic value in other conditions should at least be convincing of the advisability of further studies. Fortunately, this disturbing situation is beginning to change, and it is hoped that a review of the evidence for the effectiveness and safety of small, physiologic dosages of cortisol will help physicians to realize that physiologic dosages of cortisol are both safe and effective in a large number of clinical disorders.

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Chapter 3

THE SIGNIFICANCE OF NORMAL ADRENOCORTICAL FUNCTION

The adrenals are fascinating glands. Situated at the upper pole of each kidney, their significance has been realized only since the 1930s. Early experiments demonstrated that the removal of the adrenals of a rat produced no obvious effect so long as the animal was kept under ideal environmental conditions, viz., proper temperature, proper amounts of food, salt, water and rest at proper intervals, and avoidance of excessive exercise or infection. If any one of these environmental factors was changed, however, the animal died. It therefore became evident that the adrenal glands were necessary for adapting to changes from an ideal environment, that is, to stresses and strains.

Both morphologically and functionally, each adrenal gland consists of two sections: the cortex, or outer portion, and the medulla, or central portion. The hormones of the medulla, epinephrine (adrenalin) and norepinephrine (nor-adrenalin), are catecholamines and are primarily involved in acute responses to stress, such as fright, fear and anger. They are responsible for the increased heart rate, increased blood pressure, and mobilization of sugar from the liver to the blood stream, which prepares the organism for fight or flight.

The hormones of the cortex are steroids of which there are at least four types, and they are essential for the organism's ability to respond to more prolonged stresses such as infection, injury, starvation, and strenuous or prolonged exertion. The most important type of steroid produced by the adrenal cortex is glucocorticoid. This type of steroid has as one of its chief actions stimulation of the formation of glucose, a type of sugar that is the body's main source of energy, from non-carbohydrate sources such as amino acids from protein, a process known as gluconeogenesis. This is a vital effect in the maintenance of normal levels of blood glucose when food intake is irregular, since low blood sugar is incompatible with normal function of the brain, muscles, or other tissues

of the body. The major glucocorticoid produced in humans is cortisol (hydrocortisone), but cortisone is also produced in small amounts. Cortisone, however, must be converted to cortisol before it produces its characteristic metabolic effects. Glucocorticoids have another action that is of importance in survival under stress: the maintenance of normal vascular tone. The exact mechanisms by which cortisol brings about these critical effects are unknown. For many years cortisol levels in the urine or blood were measured as 17-hydroxycorticosteroids by the Porter-Silber reaction of the 17, 21-dihydroxy, 20-ketones, but radioimmunoassay (RIA) made possible more accurate and specific measurements of single steroids.

The second type of adrenocortical hormone is mineralocorticoid, the chief of which is aldosterone. This steroid regulates the levels of sodium and potassium in extra- and intra-cellular fluid, respectively, promoting sodium retention and potassium loss, an action that is necessary for normal fluid and electrolyte balance and for maintenance of normal blood pressure. Natural glucocorticoids also have some electrolyte-regulating effect.

The third type is androgen, represented by dehydroepiandrosterone (DHEA) and androstenedione, and their chief function appears to be promotion of growth and repair of protein tissues of the body, especially muscle. This effect is important not only in normal growth and development but also in healing of tissue damaged by injury or infection. For many years androgen levels were estimated by urinary excretion of 17-ketosteroids (17-KS), a relatively nonspecific method, since not all androgens are excreted as 17-KS and not all 17-KS are metabolites of androgens. As with glucocorticoids, radioimmunoassay has now replaced earlier methods.

The fourth type is estrogen. Adrenal estrogen seems to be mainly involved in providing a supply of this hormone during menses and at the menopause when production by the ovaries is temporarily or permanently interrupted, but it may have other, as yet unrecognized functions in growth or development. Some estrogen is produced directly in the adrenals, but estrogen may also be produced in peripheral tissues from DHEA.

A fifth type of hormone produced by the adrenal cortex seems likely, but the evidence for its existence is only indirect, and its chemical identity is not known. This possible hormone would have an

anti-sodium-retaining, or natriuretic, effect. It has been recognized for many years that patients with adrenal insufficiency not only are more susceptible to low levels of serum sodium, with resulting hypotension and shock, but are also more susceptible to pathologic sodium retention from excessive amounts of salt or of sodium-retaining steroids such as aldosterone, desoxycorticosterone, or 9-alpha-fluorohydrocortisone, suggesting that the adrenals might produce a substance that protects against excessive sodium retention.

In 1948, Wilkins and Lewis[1] suggested that a steroid promoting sodium excretion might exist as an explanation for the excessive salt loss that occurs in some patients with congenital adrenal hyperplasia. Experimental evidence for this possibility was reported in 1949 by Knowlton and his associates.[2] After producing cytotoxic serum nephritis in rats, they found that injections of 2.5 mg cortisone acetate daily in nonadrenalectomized animals produced a moderate hypertension, whereas injections into adrenalectomized animals caused severe hypertension.

Jailer[3] summarized evidence for this salt-losing adrenal hormone in 1951, and Cope[4] provided another summary in 1972. More recently, some of these effects have been thought to be explained by the actions of arginine vasopressin or of atrial natriuretic peptide, but the possibility that the adrenal cortex might produce a sodium-excreting factor has not been excluded.

Two hormones produced normally by the ovaries, progesterone and 17-hydroxyprogesterone, have been demonstrated to have natriuretic properties,[5–8] and they are known intermediary steroids in adrenal cortices in the pathway of production of cortisol, occurring in excess in certain types of congenital adrenal hyperplasia, but the possibility that they might aid in normal water balance has apparently not been investigated.

The identification of normal anti-sodium-retaining factors is of special interest because of their possible relation to some cases of hypertension. In addition to hypertension being caused by excessive sodium-retaining hormones such as aldosterone and desoxycorticosterone, it might also result from a deficiency of sodium-excreting factors.

In the unstressed state, a diurnal pattern of production of glucocorticoid and androgen occurs. A person who sleeps from 11 PM to 7 AM has a maximum level of cortisol in his or her blood at approximately 8 AM, then it gradually decreases through the day and evening, reaching a low point at approximately 1 AM, following which it increases progressively during

sleep to reach its maximum again at 8 AM the next day. The peak daily level of plasma cortisol in a normal individual is usually between 20 and 30 mcg/100 ml, and the lowest level is between 5 and 10 mcg/100 ml. This diurnal pattern is related to a person's sleep-wake schedule, and when this schedule is changed, as occurs when a person changes from one work shift to another, or when one travels to different time zones, approximately five to ten days are required before a stable new diurnal pattern of plasma cortisol level is reached. This apparently is a major factor responsible for travel fatigue or "jet lag" and it also suggests that industries that frequently change the time schedules of their workers may not be achieving maximum work effort from them but may actually be impairing their efficiency.

The significance of the diurnal pattern of corticosteroid production is not definitely known, but it is apparently related to nature's plan for restoring energy by a period of sleep in each twenty-four hours. It seems that we need a period of about eight hours sleep in each twenty-four hours to recharge our batteries. The circadian periodicity of corticosteroid production occurs in animals also. There is evidence that in the rat this periodicity becomes established twenty-one to twenty-five days after birth, but it may be suppressed by administration of corticosteroids between days two and four of neonatal life,[9] suggesting that administration of excessive dosages of glucocorticoids to infants may permanently affect their pituitary or adrenocortical function.

The production of cortisol is primarily regulated by the production of adrenocorticotropic hormone (ACTH, corticotropin) by the pituitary, which is in turn controlled by the production of corticotropin-releasing factor (CRF) by the hypothalamus. The production of DHEA seems to be only partly regulated by ACTH, but its control is less well understood.

STRESS

The importance of the adrenal cortex in response to stress is indicated by studies of the general adaptation syndrome. This is the sum of the organism's nonspecific response to stress and was intensively studied and described by Selye.[10] It has been divided into three main stages: the alarm reaction, the stage of resistance, and the stage of exhaustion. The third stage comes into play only if the alarming stimulus is sufficiently severe and sufficiently prolonged.

The alarm reaction has been further divided into an initial stage of shock and a secondary stage of countershock. Evidence indicates that during the initial stage of shock, effects characteristic of an acute release of epinephrine are followed by changes characteristic of relative adrenocortical deficiency (a fall in blood pressure, decreased blood sugar, decreased blood sodium, and increased blood potassium) lasting a few minutes to hours. The stage of countershock then occurs, with effects characteristic of increased adrenocortical activity (return of blood pressure to normal or above normal, increased blood sugar, restoration of normal or increased level of blood sodium and normal or decreased level of blood potassium; and enlargement of the adrenal cortex). These effects return to baseline during the stage of resistance but reappear during the stage of exhaustion. In hypophysectomized animals these changes do not occur, suggesting that they are mediated by the hypothalamus and pituitary gland through their production of CRF and ACTH, respectively, stimulating the production of cortisol by the adrenal cortex. During the recovery phase, and as the production of cortisol returns to normal, the production of adrenocortical androgens increases and apparently is related to the healing process. It is therefore evident that adrenocortical hormones, especially cortisol, play an important role in normal response to stress.

The critical role of the adrenal cortex in response to stress in human subjects is manifested in a number of ways. A patient with untreated mild adrenal insufficiency or low adrenal reserve may function reasonably well when environmental conditions are optimum but tends to tire more easily, and if strenuous physical exercise is undertaken or a meal skipped, hypoglycemic symptoms may develop. If an infection such as a common cold develops, symptoms tend to be more severe and last longer than in a person with normal adrenocortical reserve. These undesirable developments may be prevented by administration of suitable, safe, physiologic dosages of cortisol. It has also been demonstrated that normal adrenocortical function is essential for optimum ability to withstand infections, numerous studies having indicated that either too little or too much glucocorticoid can impair resistance to infection, whereas an optimum level of cortisol enhances resistance to infection.[11–13]

In addition to the importance of the adrenals in response to stress as a factor in survival, the effects of the adrenocortical steroids upon growth and maturation may account for many of the differences in physical

development and energy between individuals. It has been found that each person has his or her own characteristic pattern of urinary 17-ketosteroid fractions,[14] and it appears likely that this pattern, which reflects the type of steroids produced by adrenal cortices, is related to physical development, energy and gonadal function. From the time that steroid fractions were first measured in urine from individual subjects, a constancy of pattern for each person has been noted.[14–16] In 1963, Michelakis and I[14] confirmed, through a fractionation technique that measured cortols and cortolones in addition to other 17-ketosteroids in 24 hour urine collections, that normal persons have reproducible unique individual patterns of excretion of 17-KS fractions. In addition, we found that women with hirsutism or ovarian dysfunction had reproducible individual patterns that differed from those of women without these disorders, and that physiologic dosages of cortisol tended to restore more normal patterns, but stopping treatment resulted in a return to the original abnormal patterns. It therefore appears that each person has his or her characteristic pattern of excretion of these steroid fractions in the unstressed state, but significant variations of pattern occur between normal persons as well as between patients.

After administration of small doses of ACTH or corticosteroid, it became evident that some persons may have variations in pattern with different degrees of ACTH stimulation.[14] Although some subjects respond to a standard ACTH stimulus with a uniform rise in all fractions, in others the responses are asymmetrical with variations in rise of excretions of different fractions from an insignificant amount to an increment greater than average. Such differences could result from differences in production by the adrenals of steroids that are metabolized and excreted as 17-KS in the urine, or from differences in metabolism of 17-KS precursors in the liver or other tissues.

It is therefore evident that in some persons fluctuations in endogenous ACTH may alter steroid excretion patterns, whereas in others they may not. Hirsutism and acne are known to result from excess androgen, and excess estrogen can cause ovarian dysfunction. Although there is evidence that the occurrence of hirsutism, acne or ovarian dysfunction is not necessarily related to any single specific pattern of steroid excretion,[14] the variation of pattern with different levels of ACTH stimulation may be related to the clinical observation that women may develop hirsutism, acne, or ovarian dysfunction after stress.

In 1964, Prezio et al.[17] reported that resting urinary 17-hydroxycorticosteroid (17-OHST) levels correlated with lean body mass, whereas after ACTH stimulation the best correlation of 17-OHST excretion was with excess fat and total body weight, suggesting that adrenal production of glucocorticoids was related to body size and fat composition. Dunkelman and his associates[18] found that obese persons not only had increased urinary 17-OHST compared with non-obese controls but cortisol production rates were also high, plasma cortisol levels tended to be high, and response to a standard ACTH stimulus was greater than normal.

These studies suggest that individual differences in steroid production or metabolism may not only affect energy, but also influence body growth and development, and it is quite likely that they may affect the aging process, response to stress, and even the development of "stress diseases." The adrenals undoubtedly contribute to the factors that make us different individuals.

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Chapter 4

GENERALLY ACCEPTED USES OF PHYSIOLOGIC DOSAGES INCLUDING THE DIAGNOSIS AND TREATMENT OF MILD ADRENOCORTICAL DEFICIENCY

ADRENAL INSUFFICIENCY

The most logical use of physiologic dosages of cortisol is in the treatment of patients with known adrenal insufficiency. Severe examples of this disorder are manifested by hyperpigmentation of the skin, weakness, fatigue, anorexia, and susceptibility to collapse and shock with exposure to stress. This clinical picture was first described by Sir Thomas Addison in 1855 and subsequently has been called Addison's disease. For many years tuberculosis of the adrenals was its most frequent cause, but with the decreased incidence of tuberculosis resulting from improved prevention and treatment, "idiopathic" adrenal insufficiency or adrenal insufficiency resulting from an autoimmune phenomenon[1] have become more common diagnoses.

These are relatively rare disorders, however, and when cortisone and adrenocorticotropic hormone (ACTH) became available for human use in 1948, these hormones first attracted worldwide attention by their dramatic beneficial effects on patients with rheumatoid arthritis. The dosages employed were large, however, and when continued they produced undesirable and sometimes catastrophic side effects, so this treatment developed a reputation for being too dangerous for general use in patients with rheumatoid arthritis and other autoimmune disorders. This reputation has apparently caused a tendency to minimize the size of replacement dosages of steroids for patients with adrenocortical deficiency that are recommended in endocrine textbooks and sometimes even a preference for synthetic steroids over the natural hormone, cortisol.

Our rationale for the treatment of patients with adrenocortical deficiency has been based on the impression that nature usually has good

reasons for choosing the specific chemical substances secreted as hormones, and the studies illustrated in Figures 1 and 2 (pages 15 and 16) provide information indicating that a total dosage of 35 to 40 mg of cortisol daily administered in divided doses at maximum intervals of 8 hours should supply adequate glucocorticoid replacement for an unstressed adrenalectomized patient. Because patients with spontaneous adrenocortical deficiency usually seek medical care before a complete lack of cortisol develops, replacement dosages for such patients usually total less than 35 mg daily, taken as 7.5, 5, or 2.5 mg four times daily before meals and at bedtime (ac and hs). Supplementary sodium-retaining effect in the form of 9 alpha-fluorohydrocortisone (9 alpha-FF [Florinef®]), 0.1 mg daily or three times weekly, is rarely needed except in totally adrenalectomized patients.

Meanwhile, experience with the use of small, safe, physiologic dosages of cortisone or cortisol in patients with ovarian dysfunction and infertility revealed that patients with associated allergies, chronic fatigue or autoimmune disorders also reported improvement in these conditions while taking the steroid, without experiencing any undesirable side effects. These results were published in a leading medical journal,[2] but the reputation of glucocorticoids had become so bad that they received little attention. Subsequently, improved methods of diagnosis have enabled the identification of mild degrees of adrenocortical deficiency, thus providing an explanation for at least some of these beneficial effects.

Hence, the diagnosis and treatment of mild adrenocortical deficiency, a condition that is rarely mentioned in medical textbooks, has become important for all practicing physicians to recognize. It may be primary, resulting from inadequate production of cortisol by the adrenals and sometimes termed "low adrenal reserve," or it may be secondary to inadequate stimulation of the adrenals by adrenocorticotropic hormone (ACTH) from the pituitary or by corticotropin releasing factor (CRF) from the hypothalamus. Another possible cause of symptoms of cortisol deficiency is a defect in the cellular receptors for cortisol causing associated normal or elevated levels of plasma cortisol. A similar type of resistance to thyroid hormone that improved with administration of physiologic dosages of cortisol is described in Chapter 10. The recognition and treatment of these disorders is discussed in the chapters and sections devoted to them, but tests to determine the integrity of the hypothalamus-pituitary-adrenal (HPA) axis and general principles of

treatment will be discussed at this time, since they apply to all disorders of adrenocortical function, whether primary or secondary, complete or partial. The causes for these disorders are largely unknown, but they are often related to stress and inherited predisposing factors.

The symptoms and signs of severe adrenocortical deficiency are well described in standard medical or endocrine textbooks, but mild adrenocortical deficiency has received little attention. When patients with rheumatoid arthritis or with other conditions that were later identified as autoimmune disorders were found to improve dramatically with administration of large dosages of ACTH or glucocorticoids, the possibility that they might have adrenal deficiency was considered, but because they did not have the characteristic features or laboratory findings of hypopituitarism or of Addison's disease, this possibility was eventually apparently forgotten even though at least some had abnormal levels of excretion of steroids in their urine. Recent reports have presented evidence that patients with rheumatoid arthritis and several other autoimmune disorders have abnormal responses of their HPA axes to stress, so the possibility that the development of these disorders might be related to defective HPA responses seems likely. This would explain the beneficial effects of small, physiologic dosages of cortisol that have been observed in some of these patients and support the advisability of testing the integrity of this axis and the use of therapeutic trials with safe, physiologic dosages of cortisol in patients with these disorders. Many patients with chronic allergies, another condition that improves with large dosages of ACTH or glucocorticoids, also have been found to have evidence of mild adrenocortical deficiency. These findings will be discussed in more detail in subsequent chapters, and they emphasize the importance of testing for the possibility of deficient adrenocortical function, either primary or secondary, in patients with these conditions.

Because chronic fatigue is frequently the earliest symptom of mild adrenal insufficiency, and with the availability of a simple method of determining adrenal responsiveness to ACTH, patients coming to our clinic complaining of chronic fatigue without other evident cause such as inadequate rest, anemia, hypothyroidism, or chronic illness of any type have been given ACTH tests in addition to having determinations of baseline levels of plasma cortisol and of plasma ACTH. Initially, commercial preparations of ACTH were used for the tests, but subsequently Cortrosyn® (Organon), an active ACTH fraction consisting of the first

24 of the 39 amino acids of natural ACTH, which has a relatively rapid effect enabling the test to be run in 30 minutes and is less apt to cause sensitivity reactions, has largely replaced ACTH for the tests.

It is preferable to have these tests run in the morning after the patient has had adequate sleep and has not taken for a sufficient interval of time any glucocorticoid or other medication that might affect adrenal function or blood levels of cortisol, but helpful information can be obtained by running them at any time of day. A more sensitive low dose Cortrosyn test has been suggested for the diagnosis of mild adrenal deficiency,[3] but because therapeutic trials are usually justified, even in patients with apparently normal tests, sometimes it is preferable to delay further testing until a therapeutic trial has been made, especially if it might avoid otherwise unnecessary hospitalization.

It is important to be aware that test results that fall within the "normal range" do not rule out the possibility that a patient might have mild adrenal deficiency since the normal range was probably obtained from a group of people who did not have classical Addison's disease or hypopituitarism or any other known physical disorder and is rather broad. Hence, it might include persons with chronic allergies or other conditions that may be associated with mild adrenocortical deficiency. Furthermore, as previously mentioned, mild adrenal deficiency can occur secondary to inadequate stimulation by ACTH from the pituitary or by CRF from the hypothalamus. These patients may have low normal baseline blood cortisol levels that respond normally to Cortrosyn, but still improve with a physiologic dosage of cortisol. Hence, results of Cortrosyn tests within the normal range do not exclude the possibility that patients might benefit from cortisol therapy, so a therapeutic trial might still be justified.

Patients with secondary adrenocortical deficiency may need to have x-rays of the sella turcica and determinations of blood growth hormone (GH), thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH) levels because of the possibility that they might have a tumor or other lesion in this area, but most patients with this disorder do not seem to have identifiable organic lesions. Other studies that might be helpful include a complete blood count with differential, blood sedimentation rate and tuberculin test because of the possibility of an infectious process, and x-rays of the adrenal areas and chest.

For a *Cortrosyn test,* blood is drawn for baseline plasma cortisol and ACTH levels, recording the time of day. As mentioned above, although

it is preferable to perform the test in the morning when plasma cortisol levels are highest if the patient is on a normal sleep-wake schedule, adrenal responsiveness can be determined at any time of the day. The patient does not have to be fasting, although this is also preferable, but he or she should not have taken any glucocorticoid for at least 12 hours, and preferably not for several weeks, because an abnormal Cortrosyn test due to low adrenal reserve may return to normal after a short course of cortisone acetate or cortisol or probably of any other glucocorticoid, and evidence of low reserve may not return until medication has not been taken for a month or longer. After the blood for baseline cortisol and ACTH is drawn, the patient receives an injection of 25 units of Cortrosyn into the deltoid muscle of the upper arm. Thirty minutes later a second blood specimen is drawn for plasma cortisol determination. The patient is then instructed to record any change in symptoms over the next 24 hours. A normal response is considered an increase in cortisol level to at least double the baseline value, but most normal persons will have an increase greater than twofold, and patients with secondary adrenocortical deficiency will often report a transient improvement in symptoms suggesting a mild deficiency in their production of ACTH. When plasma cortisols are determined by radioimmunoassay, as was done in our laboratory, baseline plasma cortisols are normally between 15 and 30 mcg/100 ml in the morning and between 5 and 15 mcg/100 ml in the afternoon.

This test is an example of the impossibility of having strict end points in designating normal ranges of hormone levels, especially for a dynamic hormone such as cortisol, whose levels may fluctuate from minute to minute depending upon the degree of stress in addition to diurnal variation. Hence, patients with adrenal insufficiency may have plasma cortisol levels within low normal range, especially in the afternoon and evening, and patients with hyperadrenalism may have plasma cortisol levels within upper normal range in the morning. It is therefore possible that milder degrees of low adrenal reserve may not be detected unless Cortrosyn tests are performed in the morning at a time when baseline cortisol levels are maximum. Furthermore, patients vary in their susceptibility to various degrees of stress, including the stress of having injections and blood tests, so these factors must be considered in interpreting the results of tests. Hence, a diagnosis of mild adrenocortical deficiency should depend primarily on the clinical picture and therapeutic trials are often justified even when the results of tests fall within the normal range.

It is also important to bear in mind that normal ranges for baseline levels of plasma cortisol have been determined by measurements on apparently normal subjects who had no clinical evidence of hyperadrenalism (Cushing's syndrome), hypoadrenalism (Addison's disease), congenital adrenal hyperplasia (adrenogenital syndrome), or any other apparent illness. As is evident from subsequent discussion, adrenal dysfunction can be present in persons who do not fall into any of the above groups, hence so-called "normal" ranges are probably greater than those that would be obtained by excluding, for example, any subject with acne, hirsutism, or allergies, conditions that may have associated mild disorders of adrenocortical function. Adrenal insufficiency is also characterized by an elevated plasma ACTH level, but patients with low adrenal reserve and not under stress may have normal plasma ACTH, so the Cortrosyn test of adrenal response is a more sensitive method for diagnosing this disorder.

It should be emphasized that a "normal" baseline plasma cortisol and response to Cortrosyn does not rule out the possibility that a patient might improve with a physiologic dosage of cortisol, so for patients with disorders that suggest the possibility of mild adrenal deficiency, therapeutic trials with a small, subreplacement dosage of cortisol might still be helpful. Hence, inability to obtain baseline cortisol and ACTH levels and Cortrosyn stimulation tests does not contraindicate therapeutic trials with physiologic dosages of cortisol in patients with disorders that might improve with such treatment, but the demonstration of deficiency provides a clear indication for treatment.

Cortisol, like adrenalin and insulin, is a very dynamic hormone whose production can vary from minute to minute, or even from second to second, depending upon the amount of stress being experienced. This stress may be physical, mental or emotional. In the unstressed state it is normally produced on a diurnal pattern depending upon a person's sleep-wake schedule, maximum production occurring about an hour after awakening in the morning, then slowly decreasing during the day, reaching a low point about an hour after retiring at night. Since the duration of effect of each dose of cortisol is a maximum of about 8 hours, an optimum replacement schedule would have a maximum interval of 8 hours, but for several reasons most patients prefer to take four doses daily, one before each meal and the fourth at bedtime.

Because spontaneous adrenal insufficiency results from progressive destruction of adrenal tissue, symptoms appear when the process

reaches the point where remaining adrenal tissue is insufficient to maintain normal well-being. As mentioned earlier, this may require destruction of over 90 percent of the glandular tissue, but the remnant is capable of some function, so replacement dosages of cortisol in chronic adrenal insufficiency are usually less than the 35–40 mg daily that are required for the totally adrenalectomized patient. Most patients can be maintained on between 20 and 30 mg daily in divided doses. Although some patients may feel well on less than 20 mg daily, it seems preferable to give at least this much cortisol, even to patients with low adrenal reserve, because it takes the strain off of the residual adrenal tissue and provides for more functional reserve in times of stress. Under some circumstances, it appears to provide an opportunity for residual tissue to regenerate. A few patients with low reserve have demonstrated evidence of recovery of reserve after months or even years of such treatment, but most seem to require some replacement for the remainder of their lives.

In patients with adrenal insufficiency secondary to tuberculosis, the administration of cortisol was initially employed with hesitation because of the well-known anti-inflammatory effect of large doses of glucocorticoids, causing a tendency for tubercles to break down and enable dissemination of the previously walled-off tubercle bacilli. Later, when it was found that the use of glucocorticoids in conjunction with antituberculous therapy actually enhances the effectiveness of the latter, the combined use of the two types of therapy became accepted practice. A patient with adrenal insufficiency secondary to tuberculous infection, therefore, should initially receive a suitable course of antituberculous therapy in addition to replacement cortisol in physiologic dosage.

A schedule of replacement glucocorticoid therapy in adrenal insufficiency employing two-thirds of the daily dosage before breakfast and one-third before supper has been widely recommended.[4] This is based upon the characteristic diurnal variation in plasma cortisol levels, with a peak shortly after waking in the morning and a low point shortly after retiring at night. Patients with adrenal insufficiency will do fairly well on this schedule, but when we have had them compare it with the same total dosage in four divided doses, they have invariably preferred the latter. This is not surprising in view of the evidence that the half-life of cortisol in the blood is only 100 minutes, and some metabolic effects of even large doses do not last longer than eight hours.[5] Furthermore,

although plasma cortisol reaches its lowest level shortly after retiring in the evening, it begins to rise during sleep so that by the time the patient arises in the morning it is almost at its peak for the 24 hour period. Hence, instead of the twice daily dosage more closely imitating the natural diurnal pattern, it causes a peak level in the morning followed by a period of lower than normal levels in the afternoon, then a smaller peak after supper followed by lower than normal levels during sleep and at the time of awakening in the morning. It is not surprising that a schedule employing four doses taken before meals and at bedtime produces more energy and less fatigue.

A four times daily schedule also seems to result in greater decrease in pigmentation in patients with this manifestation of adrenocortical deficiency. It is therefore possible that a schedule of only two doses daily in patients with more severe deficiency may not produce sufficient feedback to prevent excessive ACTH production, and this might contribute to the tendency for some patients on this program to develop pituitary adenomas (Nelson's syndrome).[6] Longer acting derivatives of cortisone or cortisol, such as prednisone or dexamethasone, on a once daily schedule, have therefore been suggested,[4] but because nature usually has a reason for using the hormones normally produced by the body, and because extensive experience with the normal hormones in physiologic dosages has confirmed their safety and effectiveness, it seems preferable to continue their use for treatment of patients with adrenocortical deficiency, either primary or secondary, complete or partial.

The taking of any medication every eight hours or four times daily might be considered too difficult for patients to follow, but this has not been a problem with patients with mild adrenal deficiency. Their subjective improvement has been sufficient to keep most patients taking their medication regularly. Taking cortisol three times daily, or even twice daily, will produce some improvement, but for optimum benefit the four times daily schedule has usually been more helpful and easier to follow. Patients working on night shifts or traveling to different time zones will need to adjust their schedules for taking their medication to their new mealtimes and bedtimes but when they do this promptly, they often report that this adjustment seems to diminish their tendency to develop travel fatigue or "jet lag."

Some patients report that cortisone acetate seems to be less apt to cause acid indigestion than cortisol, so if it is available, it may be tried,

but since cortisone must be converted to cortisol before producing therapeutic effects, it is becoming less frequently used. Also, although a lower dosage at supper time is logical and seems to diminish a tendency to insomnia that occurs in some patients, a lower dosage at bedtime is not always desirable because with normal diurnal variation the plasma cortisol level rises during sleep to reach a peak shortly after awakening in the morning.

An undesirable effect of taking any dosage of glucocorticoid at bedtime is that it tends to cause persistent renal function during sleep, resulting in the need to get up and void once or twice during the night. This is not a serious problem, and most patients prefer this inconvenience to the morning fatigue that may result from an inadequate dose of steroid at bedtime. If the patient has sufficient adrenal reserve, the bedtime dosage may be decreased or omitted entirely without difficulty. The occasional patient who complains of inability to sleep after the bedtime dosage of glucocorticoid may be found to be taking it without milk or food, and the insomnia appears to be related to a tendency to acid indigestion aggravated by the steroid. Such a complaint can usually be corrected by taking an antacid or milk or other light nourishment at the time of the bedtime dosage.

Also, insomnia after the bedtime dosage may be related to an excessive intake of coffee or other caffeine-containing beverages that patients with chronic fatigue frequently resort to in an effort to obtain more energy. Patients with untreated or inadequately treated adrenal insufficiency seem to be tolerant of larger amounts of caffeine; hence, when suitable replacement dosages of cortisol are administered and their tolerance returns towards normal, they may develop symptoms of excessive caffeine intake. It is, therefore, wise to caution patients who are starting on physiologic dosages of glucocorticoid regarding this possibility.

Patients with chronic adrenocortical deficiency can usually be well maintained with cortisol, 5 or 7.5 mg orally before each meal and at bedtime. If a patient has a peptic ulcer or predisposition to this disorder, antacid should be taken with each dose. If this is done, the administration of physiologic dosages of cortisol may be continued with suitable ulcer therapy without preventing healing of the ulcer.[2,7] Printed instructions, such as those on page 20, are helpful for patients to keep in a prominent place at home, such as a bulletin board or refrigerator door, where they can be referred to easily.

Patients who have been totally adrenalectomized or who have more severe degrees of adrenocortical deficiency can usually be satisfactorily maintained on cortisol in a dosage of 10 mg at breakfast and lunch, 5 mg at supper, and 10 mg at bedtime. Supplementary sodium-retaining activity may be necessary, and 9-alpha-fluorohydrocortisone (9-alpha-FF, marketed as Florinef®), 0.05 to 0.1 mg daily or three times weekly, is sufficient in most cases. Patients with spontaneous chronic adrenal deficiency may not require supplementary sodium-retaining steroid unless they are given one of the derivatives of the natural glucocorticoids that has less sodium-retaining activity. Prednisone, prednisolone, triamcinolone, methyl-prednisolone, or dexamethasone are therefore less satisfactory in the treatment of adrenal deficiency, where all of the physiologic properties of cortisol, including sodium retention, are needed.

Cortisol is available commercially as 5, 10, or 20 mg scored tablets from the Upjohn Company under the trade name of Cortef®, or as 10 or 20 mg scored tablets from Merck and Company, Inc. under the trade name of Hydrocortone®. Occasionally, a patient is encountered who is allergic to one of the ingredients used by these pharmaceutical companies in the filler for tablets of cortisone or cortisol, developing an allergic dermatitis or other mild allergic reaction whenever these tablets are taken in physiologic dosage. Pharmacologic dosages, by contrast, appear to protect against these as well as against other allergic manifestations. Because these mild allergic reactions are apparently due to sensitivity to lactose or cornstarch, both of which are used in the filler of cortisone or cortisol tablets by current manufacturers, changing to a different manufacturer's product does not usually correct the problem. Sometimes prescribing 10 mg or 20 mg tablets to be broken into halves or quarters respectively to obtain 5 mg dosages with less filler may help to avoid this problem. Otherwise, capsules containing 5 mg in a non-allergenic filler are available from a few pharmacists, but some capsules may have different absorption rates from commercial tablets and this may affect their optimum schedule of administration. A few patients have been willing to take a pediatric liquid preparation of cortisol that is too sweet for many adults. Hence, if small, subreplacement dosages become more widely used, hopefully pharmaceutical manufacturers will provide tablets with non-allergenic fillers.

Surprisingly, package inserts for cortisol still do not mention the differences between physiologic and pharmacologic dosages and effects,

implying that any of the many alarming side-effects that are listed may occur with treatment at any dosage level and thus unnecessarily alarming patients who need physiologic amounts of this normal hormone in order to live normal lives! This unfortunate situation was first pointed out by Thorn in 1966 and discussed in the first edition of this book (Chapter 2, page 20) as well as in Chapter 2 (p. 18) of this edition. With the increasing potential for the use of physiologic dosages described in this book, hopefully it will be corrected soon.

In addition to supplementary sodium-retaining activity as provided by small doses of 9-alpha-FF, women with severe adrenal insufficiency may require supplementary androgen to achieve optimum strength and sense of well-being. This is not surprising since their chief source of androgen is normally their adrenals. Unfortunately, natural adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione are not generally available for clinical use, but some pharmacists have 5 mg capsules of DHEA. Otherwise, 5 mg linguets of methyl testosterone may be helpful to provide androgenic effects. As will be discussed later, there is evidence that DHEA is a better replacement androgen for adrenal deficiency than testosterone. Women's International Pharmacy in Madison, Wisconsin is an excellent source of physiologic dosages of dehydroepiandrosterone (DHEA).

When a patient with adrenal insufficiency encounters stress, additional cortisol is necessary to maintain normal health and sense of well-being. This can vary from the extra 10 mg that may be taken by the businessman who has an unusually strenuous day ahead to the several hundred milligrams per day that may be required in the presence of an acute overwhelming infection. When a patient needs additional steroid, he or she first notices a sensation of fatigue that will disappear as soon as sufficient cortisol is taken. If supplementary glucocorticoid is not taken by patients with more severe degrees of adrenal deficiency, the fatigue may progress to malaise and generalized aching similar to that experienced when a person is developing influenza. If additional steroid is still not taken, nausea, vomiting and collapse with a high fever, fall in blood pressure and shock may ensue. Before cortisone and cortisol became available, this condition was not uncommon in patients with Addison's disease and was known as an "adrenal crisis." This condition is rarely seen today, and such patients should be hospitalized where they will usually respond satisfactorily to 50 mg hydrocortisone sodium succinate

(Solu-Cortef®) by intravenous (IV) push, followed by 100 mg of Solu-Cortef in 1000 ml 5 percent dextrose in saline by continuous IV drip over eight hours. This should be followed by additional Solu-Cortef intramuscularly every six hours in doses dependent upon the patient's response. The intramuscular route is usually preferable except in cases of circulatory collapse because it permits more flexibility of other intravenous therapy and it also decreases the tendency to hypokalemia with its toxic effects that can result from excessive cortisol effects.

If the patient is unable to take oral nourishment, supplementary potassium should be given parenterally after the first liter of IV fluid to prevent hypokalemia. This can be satisfactorily achieved by adding 15 mEq potassium chloride to each liter of intravenous fluid after the first until the patient is able to take oral nourishment containing potassium such as broth or orange juice. The sodium-retaining effect of these dosages of cortisol is sufficient so that supplementary sodium-retaining steroid has not been necessary. Cortisone is not advised for parenteral administration or when rapid replacement of cortisol deficiency is needed because it must be converted to cortisol before producing physiologic effects and this may require several hours.

After the patient feels well, the dosage of cortisol may usually be rapidly tapered to a maintenance level depending upon the nature of the stress causing the acute deficiency. If the dosage is not tapered sufficiently promptly, the patient may develop a transient psychosis of a "toxic" type or hypokalemia sufficient to cause arrhythmia or weakness. The latter may be mistaken for evidence of an inadequate amount of glucocorticoid, and if more is given, the patient's condition will worsen instead of improve. If there is any question, a serum potassium level or an electrocardiogram, which will show characteristic changes with hypokalemia, should be obtained. As soon as the patient feels well, therefore, it is advisable to taper the dosage of cortisol to a maintenance level as quickly as possible. This can usually be achieved by decreasing the daily dosage by 20 mg until a satisfactory maintenance level is reached.

Hence, a patient with adrenal insufficiency under stress requires dosages of cortisol to maintain a physiologic state that would produce hypercortisolism with its well-known undesirable effects in the unstressed state. That such larger dosages are maintaining a physiologic state during increased stress is evidenced by the normal blood cortisol

that may be found between dosages in these patients, consistent with the statement of Ingle[8] that "The increased secretion of adrenal hormones serves to meet an increased need during stress and tends to maintain homeostasis rather than to disturb it. The increased secretion does not cause a state of hypercorticism such as develops when the titer of these hormones is increased artificially in the absence of need." Hence, a patient with adrenal insufficiency under stress may require dosages of cortisol to maintain a physiologic state that would produce hypercortisolism with its well-known undesirable effects in the unstressed state.

Patients with adrenal insufficiency should, therefore, be instructed to take extra cortisol when they begin to feel unusually fatigued. If they seem to be developing a respiratory infection, they should increase their daily maintenance dosage depending upon the severity of symptoms, and they should take additional steroid until a sense of well-being is restored. For most patients, doubling their maintenance dosage to 10, 15 or 20 mg four times daily is usually adequate. As soon as they feel completely well, they should return to their basic maintenance dosage. For more severe illnesses, such as acute influenza, immediately increasing the dosage of cortisol to 20 mg four times daily until they feel completely well, which usually occurs within three or four days, then decreasing to 15 mg four times daily for one day, then to 10 mg four times daily for one day, then to the basic dosage of 5, 7.5, or 10 mg four times daily thereafter, is usually adequate. In some severe illnesses, it may be necessary to increase the dosage of cortisol to as much as 120 mg daily (30 mg four times daily), in order to achieve optimum clinical improvement. Once this has been achieved, tapering the dosage by 20 mg daily until the maintenance dosage is reached has usually been satisfactory. It is also advisable for patients to contact their physician as soon as possible in order that any associated infection or other illness may be diagnosed and treated.

If their illness is associated with nausea and vomiting, as in acute gastroenteritis or "intestinal flu," cortisol should be given parenterally as soon as possible, and continued every eight hours until oral medication can be retained. Usually one intramuscular injection is adequate, but an oral dosage twice the maintenance dosage should be continued until the patient feels well. For this reason patients with adrenal insufficiency

should always have vials of cortisol (Solu-Cortef®), with sterile syringes and needles for parenteral administration in their homes, and if they are traveling, in their personal luggage, and they and members of their families should be instructed in their use.

Because it is difficult and expensive to obtain medications away from home, patients should be advised to take at least two supplies of their medications, including hydrocortisone sodium succinate (Solu-Cortef, the Upjohn Company) in Mix-O-Vials with sterile syringes and needles, when they are traveling. One supply should be packed in their luggage, and one should be carried on their person. Hence, if one is lost, the other is available. This is especially important on trips outside the United States.

Patients with adrenal insufficiency should also be cautioned to carry identification cards stating their diagnosis, treatment, and the name, address, and telephone number of the physician to be notified in case of an emergency. Medic-Alert (the Medic-Alert Foundation, 1-800-432-5378) bracelets or necklaces are very good for this type of identification. Such information might be life-saving in case of an accident in which the patient is rendered unconscious, and it is always helpful for any physician who does not know the patient's medical history. Children taking physiologic dosages of cortisol should be given notes to their teachers and school nurses stating their diagnoses and treatment and their need to take a dosage at lunchtime. If they can be maintained on an every eight hour program, this might avoid their having to take a dosage during school hours.

When patients with adrenal insufficiency are treated according to these principles, they can live perfectly normal, healthy lives. In some respects they seem to be healthier than many persons without adrenal insufficiency in that they often appear to have more energy, less fatigue, and a greater resistance to at least some types of infection. This will be discussed in greater detail later, but at this point it should be noted that when adrenally insufficient patients with common respiratory infections are treated according to these principles, no increased incidence of complications occurs, and antibiotic therapy is not necessary nor advisable unless a bacterial infection is present; otherwise, he or she may unnecessarily become resistant to that antibiotic at times of future infections.

A review of several case histories may be helpful in understanding some of the therapeutic points that have been mentioned.

Case 1

The first patient with adrenal insufficiency to be treated with cortisone in our clinic was a young woman who was seen initially in 1949 at the age of twenty-nine years complaining of progressive weakness, malaise, and diarrhea of approximately six months duration. Increased pigmentation of her skin, absence of axillary hair, and low blood pressure strongly suggested adrenal insufficiency, and failure to respond to ACTH with a decrease in circulating eosinophils was consistent with that diagnosis. Present methods of measuring plasma cortisol and ACTH were not available then. There was no history of tuberculosis or evidence of this disease, so a diagnosis of Addison's disease of unknown etiology was made.

The patient was initially treated with desoxycorticosterone acetate pellets implanted subcutaneously, plus increased salt intake and frequent feedings. Later, methyl testosterone, one 5 mg linguet daily, was added with considerable improvement in her strength and energy. In 1951, when cortisone acetate became available for general clinical use, it was added to her therapy, but because she was our first patient with adrenal insufficiency to receive this medication for maintenance therapy, an optimum dosage schedule was not known.

Initially the patient was told to take a single dose of 12.5 mg daily. Later this was increased to 12.5 mg twice daily with impressive symptomatic improvement, then to 12.5 mg every eight hours with further improvement, but she did not reach an optimum clinical state until she received a dosage of 10 mg before each meal and 5 mg at bedtime. In 1957, 9-alpha-FF was given orally in place of the subcutaneous desoxycorticosterone pellets, and a dosage of 0.05 mg three times weekly achieved adequate supplementary sodium-retaining effect while she was receiving the 35 mg of cortisone acetate.

The patient was told to double her dosage of cortisone acetate in the event of the development of an upper respiratory infection, but later it became evident that an increase in dosage to 80 mg daily (20 mg four times daily) enabled her to recover from respiratory infections more quickly, and an increase to 120 mg (30 mg four times daily) enabled her to withstand an attack of acute influenza without serious problems. The patient's previous history was interesting in that after she had had one full-term delivery, her menstrual periods had stopped several years before she developed symptoms of adrenal insufficiency. Urinary gonadotropin excretion was normal. A dosage of 1.25 mg of conjugated estrogens daily for three weeks on and one week off produced regular withdrawal menstrual flow. At age forty-five, urinary gonadotropins were elevated, so cyclic Premarin®, 1.25 mg daily, was continued until age fifty-six. She was last contacted at age fifty-eight, when I retired from full-time practice. At that time she was apparently healthy with normal energy and strength.

This patient demonstrated the benefit of androgen administration to women with adrenal insufficiency, with further improvement from cortisone acetate, but this had to be given in four divided doses to achieve an optimum therapeutic effect. Her clinical course also demonstrated that

an increase in cortisone dosage to 80 mg daily enabled her to recover from respiratory infections with little difficulty, and an increase to 120 mg daily enabled her to withstand acute influenza without serious problems. With the now known relationship between adrenocortical and ovarian function, it is possible that her amenorrhea may have been related to her adrenal disorder, but replacement dosages of estrogen were continued up to the menopause, so there was no opportunity to observe whether normal ovarian function might have resumed with cortisone therapy in a manner similar to that of other patients (Cases 3 and 4). She further demonstrates that a patient with adrenal insufficiency can live a relatively normal life with suitable replacement therapy, since she was still quite well twenty-nine years after the condition was diagnosed.

Case 2

This case is an example of a combination of several hormone disorders, including primary adrenal insufficiency. The patient was a fifty-seven year old woman who, at age seventeen, had a hyperactive goiter removed surgically. About two years later, she developed malaise and easy fatigue and began having upper respiratory infections that lasted a month or more. At age twenty-two, she developed acute appendicitis; when an appendectomy was performed, she suffered postoperative collapse, but she recovered with general supportive measures.

Easy fatigue and frequent respiratory infections persisted, until at age twenty-seven a diagnosis of Addison's disease was made. No prior history of tuberculosis in the patient or in her family was known. Desoxycorticosterone acetate pellets were implanted subcutaneously. Menses were somewhat irregular. She was married at age twenty-nine, used no precautions, but had no pregnancies. In 1953, at age thirty-two, cortisone acetate therapy was started at another clinic in a dosage of 12.5 mg every twelve hours with occasional increase for malaise. She not only felt better, but had no respiratory infections for the next six or seven years. At age forty a recurrence of hyperthyroidism was treated with radioactive iodine.

At age forty-seven, shortly after she was referred to me, she had an attack of influenza with a temperature of 102°. Her cortisone dosage was increased to 12.5 mg four times daily, and she recovered uneventfully. She felt so much better during her convalescence when she was taking 7.5 mg of cortisol four times daily that this dosage was continued. She not only had more energy than she had while taking 12.5 mg twice daily, but her skin pigmentation decreased for the first time. Because hypothyroidism developed following radioactive iodine treatment, l-thyroxine (Synthroid®), 0.05 mg daily, was added.

At age forty-nine a nodule was noted in the right breast, and at surgery, which was undertaken less than a week after the nodule was first noted, carcinoma was found in both breasts with metastatic involvement of the nodes in the left axilla. A bilateral radical mastectomy was performed, followed by postoperative radiation

therapy to the axillae and chest. At the time of surgery, supplementary hydrocortisone sodium succinate was administered in a dosage of 100 mg intramuscularly one hour preoperatively and every eight hours for two doses following surgery, and subsequently gradually reduced. Because postoperative irradiation was administered, she was given 20 mg cortisol orally four times daily until this therapy was completed. She was subsequently maintained on cortisol 7.5 mg four times daily, and there was no evidence of recurrence of her cancer during the ensuing seven years. Menses tapered and stopped at age fifty-one. At age fifty-three, her blood FSH was 121 mIU/ml, blood estrogen was 28.0 pg/ml, T_3 sponge uptake was 45%, and T_4 was 6.4 mcg%.* She experienced moderately severe hot flashes and some arthritic symptoms, but otherwise felt well and was living a normal life at the time I retired from full-time practice when she was age fifty-six.

This is an example of the occurrence of spontaneous Graves' disease, a known autoimmune disorder, and spontaneous adrenal insufficiency, a possible autoimmune disorder, in the same person. The history of irregular menstrual periods and infertility indicates some abnormality of the pituitary-ovarian axis, and the development of carcinoma in both breasts around the time of the menopause raises a question whether this disease might also be related in some way to her other endocrine abnormalities. In spite of these serious diagnoses, she has lived a relatively normal life for seven years following radical mastectomy. The increased incidence and severity of respiratory infections prior to treatment of her adrenal insufficiency contrasted with the increased resistance to such infections while taking cortisone acetate or cortisol. This possible relationship is discussed further in Chapter 9.

Case 3

This case is another example of spontaneous adrenal insufficiency that demonstrates the subtle relationship that exists between function of the adrenals, ovaries, and thyroid glands. The patient was referred at the age of twenty-eight years because of amenorrhea following discontinuance of an oral contraceptive. The menarche had occurred at age thirteen, and cycles had been regular at monthly intervals, menses lasting five to six days. She had been married at age twenty and had full-term caesarean sections at ages twenty-one, twenty-two, and twenty-three years. She did not nurse any of her babies. After her third section, she required a transfusion and experienced a transfusion reaction. Subsequently she felt chronically fatigued. After one spontaneous menstrual flow, she was given an oral contraceptive cyclically for about fifteen months. When this was discontinued, spontaneous menses did not

*Normal ranges for tests in Case Summaries are listed on p. 187.

resume. Withdrawal bleeding occurred after various progestational agents. Occasional hot flashes were experienced, but she also was sensitive to cold. Her energy had continued to be poor. Salpingograms and a D & C had been reported normal. Her previous history had been negative except for a tonsillectomy at age six. Her mother had a total hysterectomy for an unknown cause at age thirty-four.

Physical examination was within normal limits with a height of 62 inches, weight 101½ pounds, blood pressure 95/70, and pulse 72 and regular. Urinary 17-KS were 1.5 mg/24 hours and urinary cortisol metabolites (similar to 17-OHST) were 2.3 mg/24 hours, both definitely low values. Urinary gonadotropins were within normal limits. After 80 units of ACTH gel intramuscularly, urinary 17-KS and cortisol metabolites did not change significantly, consistent with the presence of primary adrenal insufficiency. On cortisol (Cortef) 5 mg four times daily, she experienced marked symptomatic improvement and a resumption of spontaneous menses. These occurred at irregular intervals, however, so the dosage of Cortef was increased to 7.5 mg four times daily. Cycles were still irregular, so Euthroid®, gr 1 daily, was added even though thyroid tests were within normal limits: T_3 index = 0.91 (normal 0.8–1.2), T_4 6.6 mcg% (normal 5.0–10.0). Serum cholesterol was slightly high, however, (266 mg%, with a normal range of 150–260 mg%), and she was sensitive to cold. On this program she conceived in 1972 and had a full-term caesarean section nine months later. During her pregnancy, she took cortisol, 10 mg four times daily, and Euthroid, gr 1 daily. Her obstetrician had her discontinue the Euthroid in the eighth month.

After delivery, the patient received an injection to inhibit lactation, since she was not nursing her baby. Cortisol was resumed in a dosage of 10 mg four times daily. She returned to my office four months later without having had any spontaneous menses, and she failed to have withdrawal flow after medroxyprogesterone acetate (Provera®), 5 mg daily for five days. The dosage of cortisol was decreased to 5 mg four times daily, and she resumed spontaneous menses about a month later, but her cycles were quite irregular.

Six months later an ACTH test revealed a baseline plasma cortisol at 10 AM of 21.5 mcg% (2½ hours after her last dose of 5 mg cortisol). An hour after an intramuscular (I.M.) injection of 25 units of ACTH, the plasma cortisol was 28.2 mcg%, consistent with persistent adrenal insufficiency.

The dosage of cortisol was increased to 10 mg before breakfast and lunch, 5 mg before supper, and 10 mg at bedtime, with improvement in energy, but the patient read newspaper and magazine articles about the dangerous effects of cortisone therapy so she kept skipping doses and trying to wean herself off the medication. Each time she did this, she developed increased fatigue and malaise, so treatment was resumed. In 1976, another ACTH test performed with an I.M. injection of 25 units of Cortrosyn again failed to demonstrate an adrenal response. Plasma follicle-stimulating hormone (FSH) at that time was normal, but T_3 sponge uptake was 37% (normal 40–60%), and T_4 was 3.6 mcg% (normal 4.0–10.0). Because she had no symptoms of hypothyroidism, T_3 by RIA was measured, and this was 155 ng/100 ml, a value well within normal limits (90–200).

She therefore not only had adrenal insufficiency, but also evidence of abnormal thyroid function characterized by a low T_3 sponge uptake and T_4 with a normal triiodothyronine level in the blood.

She failed to return for follow-up until two years later. During the previous year, she had repeated respiratory infections and had become more sensitive to cold. T_3 sponge uptake was 35%, T_4 3.3, and T_3 by RIA had decreased to 20 ng/100 ml. The diagnosis of hypothyroidism was no longer in question, and Euthroid, gr 1 daily, was resumed with restoration of normal health and regular menses.

That this patient developed adrenal insufficiency after a transfusion reaction following her third caesarean section raises a question of possible etiologic relationship. Could the transfusion reaction have initiated an autoimmune process that damaged her adrenals and possibly also her thyroid gland? She later developed post-contraceptive pill amenorrhea with normal FSH, and she resumed menses and conceived when replacement cortisol and thyroid therapy were administered, subsequently having another full-term, normal pregnancy. Her obstetrician did not maintain communication with her endocrinologist during her pregnancy and delivery, and this may have affected her postpartum course, since it is usually advisable for patients to continue physiologic dosages of cortisol and thyroid up to the time of delivery, then resume these medications postpartum in the dosages the patient was taking at the time she conceived.

The resumption of menses postpartum was apparently affected by her replacement dosage of cortisol and probably also by the cessation of thyroid medication. Post-contraceptive amenorrhea is now known to be sometimes associated with an elevated level of plasma prolactin, but a test for it was not available at that time. She had no evidence of persistent lactation, however. Although she did not resume thyroid medication postpartum, she did not develop definite clinical evidence of hypothyroidism until six years later, and her menstrual cycles did not become regular until thyroid replacement therapy was administered in addition to cortisol. She is one of numerous patients who have become alarmed by literature that emphasizes the hazards of glucocorticoid therapy without mentioning that cortisol is a natural hormone necessary for normal health and energy.

Case 4

This patient was totally adrenalectomized for Cushing's syndrome. The young woman was referred in 1967 at the age of twenty-four years with a chief complaint

of rounding of her face and increased hair growth for the previous year. The menarche had occurred at age thirteen, and her cycles had always been irregular with intervals of thirty to sixty days, menses lasting five days without cramps. She had been married seven years previously and had a daughter six years old. She had had no difficulty conceiving and her pregnancy was normal. She did not nurse her baby, and menses resumed uneventfully.

Four impacted wisdom teeth had been removed at age twenty-one, and the patient thought her problems started after this dental surgery. For two years prior to her initial visit, she had been more nervous, changed from being sensitive to cold to sensitive to heat, and developed diarrhea about once weekly. During the previous year, she had noted more rounding of her face and some increased hair growth on her face. A gynecologist had performed a wedge resection of her ovaries 6 months before her visit. The ovaries were said to be only slightly enlarged, but bilateral cysts were present. Her menses continued to be irregular. Her weight had increased from 115 to 122 pounds over the previous year. Her mother and maternal grandmother had had thyroid operations, and her maternal grandmother also had diabetes mellitus. There was no family history of hypertension.

Physical examination revealed a young woman with definite rounding of the face and moderate hirsutism of the face and periareolar areas. Height was 63¼ inches, weight was 122 pounds without shoes. Mild acne was present on the shoulders and back, but there were no striae. Blood pressure was 165/105, pulse 96 and regular. The thyroid was not enlarged, and there was no lymphadenopathy. Breast development was normal with slight deep induration on the right. There was no edema, and no bruises were present. The remainder of her examination was not remarkable. Plasma cortisol at 8 AM was 23.0 and at 4 PM was 31.8 mcg%. Urinary 17-KS were 19.6 and cortisol metabolites 22.5 mg/24 hours. A brisk response to ACTH stimulation occurred, and dexamethasone suppressed plasma cortisol and urinary 17-KS and cortisol metabolites to normal. An x-ray of the skull showed no enlargement of the sella turcica. A diagnosis of Cushing's syndrome with adrenal hyperplasia was therefore made.

She was given sufficient dexamethasone to keep her steroid levels normal, but her adrenals continued to become hyperactive whenever the dosage of dexamethasone was decreased, and cushingoid features worsened while she was taking this medication. A total bilateral adrenalectomy was therefore performed at age 25. Postoperatively she was maintained on cortisol, 10 mg four times daily, and a 9-a-FF, 0.1 mg three times weekly. After surgery, her blood pressure became normal but gradually increased from 130/85 to 140/100, so the 9-a-FF was tapered and discontinued. Hydrodiuril®, 50 mg daily, and later Inderal®, 10 mg four times daily, caused the blood pressure to decrease to 125/90. After approximately a year, the hydrochlorathiazide was discontinued without significantly affecting the blood pressure, and later Inderal was discontinued. For the next three years, her blood pressure varied between 120 and 140/80 to 100 with no antihypertensive medication.

In spite of her maintenance therapy, the patient continued to complain of chronic fatigue, so a month after adrenalectomy, dehydroepiandrosterone (DHEA), 5 mg by

mouth twice daily, was started. A limited supply of this steroid had been provided by Ayerst Laboratories for clinical investigation. This produced impressive improvement in her energy, and she developed spontaneous menses at monthly intervals, the first time she had ever had regular menstrual cycles. Because our supply of DHEA was limited, it was discontinued after she had achieved optimum clinical improvement on four different occasions. Each time the steroid was stopped, fatigue and irregular menses returned, sometimes associated with functional bleeding, and she also noted that she bruised more easily when she was not taking this steroid.

When it was resumed, energy improved, menstrual cycles became regular, and she no longer bruised easily. Other androgens, including methyl testosterone, Halotestin®, and testosterone propionate were tried, but none of these restored normal menses or produced as much improvement in energy as the DHEA. Vitamin C, 100 mg daily, was also tried, but it did not produce the clinical improvement noted with DHEA.

Follow-up skull x-rays were normal. At age 30, five years after adrenalectomy, her pigmentation, which had increased initially, appeared to be definitely subsiding. Urinary FSH was 10 mouse uterine units (m.u.u.) and total estrogens 29 μg/24 hours, both within normal limits for a female. She was not taking DHEA at the time of these tests. Six years post-adrenalectomy, plasma ACTH by RIA was 49.9 pg/ml (normal 15–100). The following year, at age 42, her medication was changed from cortisol to cortisone acetate, 10 mg before breakfast, lunch and at bedtime, and 5 mg before supper, and she thought this caused less tendency to indigestion.

In October 1975, our supply of DHEA again was exhausted, and shortly after that her menses ceased and she noted increased fatigue. Later, methyl testosterone, one 5 mg linguet daily, or Halotestin, 2 mg daily, seemed to restore strength and menses, but not as well as DHEA. Two years later (nine years post-adrenalectomy), plasma DHEA-S (dehydroepiandrosterone sulfate) was 13 mcg/dl (normal 80–390 mcg/dl). A new supply of DHEA, 5 mg daily, helped restore energy and regular, normal menses. Emotional problems related to various stresses incurred in raising a family developed, but slight changes in dosages of cortisone and thyroid seemed to help, and she was eventually stabilized on cortisone acetate 15-15-10-10, DHEA 5 mg daily, and Euthroid, gr 1 before breakfast and gr ½ before supper daily.

Nineteen years post-adrenalectomy, at age 44, our supply of DHEA was again exhausted, but Halotestin, 2 mg daily, seemed to help almost as well, with a continuation of regular menses and adequate energy and strength. In 1996, she was age 51 and living an apparently normal life on her replacement therapy of cortisone acetate, 15-15-10-10, Halotestin, 2 mg daily, and Euthroid-1, twice daily.

This patient has been followed for twenty-six years after a total bilateral adrenalectomy for Cushing's syndrome. Although she has lived a reasonably normal life, evidence was impressive that supplementation with DHEA provided better replacement than other commercially available androgens. Andrews[9] has reviewed the experimental evidence for possible mechanisms of reproductive suppression by increased ACTH

secretion, but it also appears that a deficient production of DHEA may have a similar effect.

DHEA is a normal hormone that is apparently produced in larger quantities under unstressed circumstances than any other adrenocortical hormone, yet very little is known about its contribution to normal health, presumably due to its failure to be protected by a patent. It is a relatively weak androgen, but it is a precursor of both estrogen and testosterone, and observations such as those made on this patient indicate that its deficiency can interfere with normal ovarian function. While pharmaceutical companies are investing millions into the development of new medications, it is surprising that no attempt has been made to determine the potential value of this normal hormone that has been known for over 40 years to the maintenance of optimum health.

MILD ADRENOCORTICAL DEFICIENCY

As mentioned previously, mild adrenocortical deficiency, either primary (low adrenal reserve) or secondary to inadequate stimulation by the pituitary or the hypothalamus, is another clinical disorder in which physiologic dosages of cortisol have a rational role in therapy. Low adrenal reserve is characterized by a subnormal response to ACTH with baseline plasma cortisol level within normal range. Because of their residual adrenocortical function, patients with this disorder can sometimes omit the bedtime dose of cortisol. Mild secondary adrenocortical deficiency is characterized by a baseline plasma cortisol level either low or in the low normal range, but with a normal response to Cortrosyn stimulation.

An impressive number of patients with unexplained chronic fatigue have been found to have mild adrenocortical deficiency, either primary or secondary, and the administration of cortisol in a dosage of 5 mg four times daily has resulted in clinical improvement that is often dramatic. Many of these patients have been studied intensively prior to being referred for endocrine evaluation, receiving various other types of therapy, including vitamins, iron, and thyroid medication, without benefit. That many had been told their fatigue must have a psychogenic basis when previous studies had failed to demonstrate any evidence of organic disorder emphasizes the importance of this condition.

Patients with psychiatric disorders, especially anxiety and depression, frequently complain of chronic fatigue, but their baseline plasma

cortisols tend to be high and their adrenals characteristically are hyperresponsive to ACTH,[10,11] so a Cortrosyn test should distinguish them from patients with mild adrenal deficiency. Patients with mild adrenal deficiency describe wanting to do things but feeling too exhausted to undertake them, and they usually present no evidence of serious psychologic problems. Their fatigue is usually present throughout the day, often being noted when they first awaken in the morning, whereas the fatigue complained of by hypothyroid patients often does not develop until afternoon or evening. Patients with known psychologic problems who complain of fatigue should also have Cortrosyn tests, because in some cases it appears that the chronic fatigue resulting from mild adrenal deficiency has aggravated a psychic disorder, and if the chronic fatigue can be helped, the psychologic disorder may also be benefited. Other conditions that often are associated with mild adrenocortical deficiency are functional hypoglycemia (Chapter 10), allergic disorders (Chapter 7), and autoimmune disorders (Chapters 6 and 8).

The etiology of mild adrenal deficiency is not known, but it is interesting to note that heavy cigarette smoking[12] and ingestion of moderate amounts of coffee[13] have been found to cause significant rises in plasma and urinary 11-hydroxycorticosteroid concentrations, possibly due to enhanced ACTH release resulting from nicotine—or caffeine—induced increase in sympathetic and catecholamine activity. Whether prolonged adrenocortical stimulation from these or other causes could result in mild adrenal deficiency in susceptible persons remains speculative.

The possibility that ascorbic acid deficiency might cause low adrenal reserve should also be studied. The highest concentration of ascorbic acid in the body occurs in the adrenal cortex, but its function there has never been elucidated. Presumably it plays a role in the production of adrenocortical steroids. Administration of large dosages of vitamin C has been reported to have a protective effect against the common cold as well as some other beneficial effects that have been noted with physiologic dosages of cortisone or cortisol,[14] so a relationship would not be surprising.

It should be emphasized that clinical improvement from physiologic dosages of cortisol may not become evident for up to two weeks after the initiation of this therapeutic program, so patients should be cautioned not to become discouraged if they do not feel better immediately.

Even though plasma cortisol and ACTH levels and response to Cortrosyn stimulation tests may be within normal range, patients with

unexplained chronic fatigue may still warrant therapeutic trials with a small dosage of cortisol since the interference with normal daily living described by these patients is sufficient to warrant careful investigation, and since the chances of restoring energy and a sense of well-being seem to be quite good.

Several case histories provide examples of the value of this type of therapy in patients with low adrenal reserve.

Case 5

The patient was a fifty-six-year-old female who had experienced episodes of nausea and fainting for approximately twenty years. At first, these episodes would occur at intervals of one or two years, but at about age fifty-four they became more frequent, as often as once a week. They were usually associated with headache. At age fifty-four, she was admitted to a hospital where a neurological consultation reported no evidence of abnormality, but blood sugar was noted to be low three hours after glucose administration during a routine glucose tolerance test. X-rays of the skull, and brain and liver scans were all normal, and she was discharged with a diagnosis of functional hypoglycemia.

After discharge, she experienced little benefit from dietary therapy and began to complain of chronic fatigue as well, so at age fifty-six she was referred for an endocrinologic evaluation. Because she was receiving medications including Dilantin®, Bellergal®, and Pro-Banthine®, some of which might interfere with plasma cortisol determinations, and because her symptoms were somewhat suggestive of adrenal insufficiency, she was given a therapeutic trial with cortisol, 5 mg four times daily.

She returned two weeks later reporting dramatic improvement. She was, therefore, tapered off of all medications. A week after discontinuing cortisol, her plasma cortisol at 9 AM was 19.3 mcg%, and one hour after an I.M. injection of 25 units of ACTH this rose to 38.2 mcg%, an apparently normal response. She developed weakness and fatigue off the medication, however, so cortisol was resumed in a dosage of 5 mg four times daily, with another impressive subjective response.

It was therefore decided to obtain a metopirone test to check on the possibility of hypopituitarism causing her symptoms, but this test also was within normal limits. Cortisol had been discontinued the day before the metopirone test was started. She was then instructed to discontinue the cortisol for six weeks, following which a second ACTH test showed very clear evidence of low adrenal reserve, with a baseline plasma cortisol level of 21.7 mcg% at 9 AM and a rise to only 26.7 mcg% after ACTH. Meanwhile, she had again developed symptoms of frequent headaches, nausea, chronic fatigue, and malaise. She again improved after the resumption of cortisol, 5 mg four times daily.

The patient still tired somewhat easily, however, and when she developed an upper respiratory infection and her dosage was increased to 10 mg four times daily, she stated she felt so much better that her maintenance dosage was increased to 7.5 mg

four times daily. She has continued to feel quite well on this dosage. At the time of this report she had received this therapy for a total of five years, during which time she had no undesirable side effects and felt better than she had for many years. She experienced several respiratory infections, but when her dosage was doubled, she recovered promptly. On two occasions, she was given penicillin and on two occasions erythromycin for sinusitis during this period.

This case demonstrates how unexplained nausea and faintness, especially when associated with functional hypoglycemia, should suggest the possibility of adrenal insufficiency. It also demonstrates how therapy with glucocorticoid can result in a temporary restoration of adrenal reserve that may relapse after glucocorticoid is withheld for several weeks. In addition, she provides an example of how respiratory infections can be well tolerated with the therapeutic glucocorticoid program recommended.

Case 6

This patient was a fifty-one-year-old female. She had reached the menarche at age fourteen with regular cycles at intervals of twenty-eight days until she went to college, when menses ceased. They resumed at the time of spring and summer vacations, however, consistent with a diagnosis of "psychogenic amenorrhea." She was married at age twenty-two, used no precautions, but was unable to conceive. Her husband was found to have a low sperm count, so they adopted two children.

At age forty, the patient had operations for bilateral inguinal hernias, and the surgeon noted the presence of endometriosis, so a few months later a hysterectomy and bilateral salpingo-oophorectomy were performed. She was given Premarin, 0.625 mg daily on a cyclic schedule, but hot flashes persisted, so the dosage was increased to 1.25 mg cyclically. This corrected the hot flashes, but she developed intermittent stiffness and aching in the knees and other joints, and she tended to tire more easily.

For several years the patient had noted numbness in her hands and toes after exposure to cold and after sleeping, and this became worse. Her skin tended to be dry, and she had mild constipation. T_3 sponge uptake and serum thyroxine were normal, but an ACTH test revealed low adrenal reserve with a baseline plasma cortisol of 19.4 mcg% at 9 AM and a rise to 25.9 mcg% thirty minutes after an I.M. injection of Cortrosyn. Cortisol, 5 mg four times daily, was started, and within two weeks she noted marked subjective improvement with normal energy, disappearance of arthralgias, and a general increase in sense of well-being. Cyclic Premarin therapy was maintained.

The patient continued to feel well over the subsequent five years and she also reported increased resistance to respiratory infections. Whenever symptoms of incipient respiratory infections developed, the dosage of cortisol was doubled until the symptoms cleared. On several occasions, symptoms disappeared within

twenty-four hours with such therapy, suggesting that the illness had been aborted. During this time her husband had numerous respiratory infections, so there had been no apparent change in her exposure to such infections.

This patient's low adrenal reserve was initially manifested by intermittent arthritic symptoms as well as chronic fatigue following a surgical menopause. This condition has been termed "menopausal arthritis," and this patient's experience indicates the advisability of testing adrenal responsiveness in such patients. Improvement with small physiologic dosages of cortisol may be dramatic. It is tempting to speculate that the "psychogenic amenorrhea" was a manifestation of the increased stress of attending college interfering with normal pituitary-ovarian function, a disorder that may be corrected by the administration of small dosages of cortisol. Later, after bilateral herniorrhaphy and bilateral salpingo-oophorectomy, the increased demand upon the adrenals may have resulted in symptoms of fatigue and arthritis that were corrected by cortisol administration. Cyclic Premarin therapy was continued because she had not yet reached the usual age of spontaneous menopause. She had no further symptoms of endometriosis. She is one of numerous patients who have reported evidence of increased resistance to respiratory infections while taking small doses of cortisol, and this will be discussed in more detail in Chapter 9.

Another example of low adrenal reserve is presented in case number 7.

Case 7

A fifty-nine-year-old female had been experiencing episodes of fatigue since the age of forty-six. Her menstrual history had been normal until age thirty-five, when she developed prolonged uterine bleeding. Radium therapy to the endometrium had been administered for this, and she developed subsequent amenorrhea and hot flashes. The episodes of fatigue began about ten years later. Her previous physician had given her dexamethasone for four days empirically with suggestive benefit. Later, when her symptoms returned, she had been given various other medications, including estrogen and androgens, without apparent effect. She had also been given thyroid medication without benefit. Four months prior to her referral, she had been given prednisone, 5 mg twice daily with dramatic improvement, but when the dosage was reduced to 5 mg daily, fatigue returned. She was therefore referred as a possible case of adrenal insufficiency.

Because the patient had been taking prednisone, an ACTH test was not performed initially, but her medication was changed to cortisol in decreasing dosages. It was found that she felt best on a dosage of 7.5 mg four times daily. While receiving that dosage, she had an ACTH test that demonstrated a plasma cortisol at 10 AM

of 13.7 mcg%; one hour after an I.M. injection of 25 units of ACTH this rose to 22.9 mcg%, consistent with a sluggish adrenal response. She has subsequently felt quite well on 7.5 mg four times daily. On several occasions when the dosage was decreased to 5 mg four times daily, fatigue returned, and various aches developed, especially in her shoulders and neck.

In 1975, a return of chronic fatigue occurred while the patient was taking cortisol, 7.5 mg four times daily, and it was found that she had an infected tooth. Energy returned after the dental infection was treated. She gave a history of having never had upper respiratory infections or influenza during her lifetime, nor did she have any incidence of these infections while she was taking cortisol. She had two episodes of urinary tract infection, but these responded promptly to cephalosporin therapy. Later she had an uneventful vaginal repair of a rectocele and enterocele with a perineorraphy, receiving additional cortisol prior to and following her surgery. An ACTH test performed during her hospitalization showed persistent low adrenal reserve.

This is another patient who had developed symptoms of fatigue in her mid forties, which ultimately proved to be due to low adrenal reserve. She had experienced menopause following pelvic irradiation ten years previously. She also noted various aches and arthritic symptoms associated with chronic fatigue, and all of these symptoms were corrected by suitable physiologic dosages of cortisol. Later, the return of symptoms while she was taking cortisol was found to be due to the development of a dental infection, emphasizing the importance of looking for obscure infections in patients who have a relapse of symptoms while taking a dosage of steroid that has previously been sufficient to control their condition. This patient is also one of several patients whom we have encountered who give a history of never having had respiratory infections or influenza, suggesting the presence of an immune mechanism that provides greater than usual resistance to this type of illness. Her case is another example of how patients with adrenal insufficiency or low reserve can tolerate elective surgery uneventfully provided they are given additional cortisol prior to and following the stress.

CONGENITAL ADRENAL HYPERPLASIA

Another disorder in which treatment with physiologic dosages of cortisone or cortisol is obviously indicated is congenital adrenal hyperplasia. This condition results from a relative deficiency of one of the enzymes in the pathway of production of cortisol in the adrenals. The deficiency in cortisol production leads to increased ACTH stimulation that in turn

causes an excessive production of those steroids that do not require the deficient enzyme. The most common defect is in 21-hydroxylase, the enzyme that converts 17-alpha-hydroxyprogesterone to cortexolone. This deficiency is usually relative rather than absolute so that the adrenals produce an excess of androgen and other steroids that do not require this enzyme in order to supply sufficient cortisol. The clinical picture is most obvious in young girls who, as a result of androgen excess, have abnormal development of the genitalia with enlargement of the clitoris, rapid skeletal growth in early childhood but premature closure of the epiphyses, resulting in ultimate short stature, androgenic build, acne, hirsutism, and poor secondary sexual development with amenorrhea and hypoplasia of the breasts.

Treatment of the disorder consists of the administration of sufficient cortisone acetate or cortisol to reduce the excessive levels of androgen and ACTH to normal. The maximum maintenance level for the unstressed patient should therefore be 35–40 mg daily of either cortisone acetate or cortisol, and many patients can be maintained on smaller dosages. Earlier reports suggested that larger doses might be necessary, but this was probably due to a suboptimum dosage schedule. Although these patients usually tolerate stress without developing adrenal insufficiency, they should be instructed to increase the dosages with stress in a manner similar to patients with adrenal insufficiency so as to avoid an excessive production of androgen during the stress.

With suitable therapy, patients with congenital adrenal hyperplasia will develop normally and be able to bear children provided treatment is instituted early and taken regularly in an optimum dosage. Even when treatment is started later in life, improvement is usually impressive, but fertility is less predictable. The schedule of dividing the daily dosage into four equal doses to be taken with meals and at bedtime provides a more effective suppression of excessive androgen production than a schedule of only two doses daily (Fig. 4).[15]

Because 21-hydroxylase is also necessary for the production of sodium-retaining steroids, there is no excess of these steroids in 21-hydroxylase deficiency. In a less common type of congenital adrenal hyperplasia due to a relative deficiency of 11-beta-hydroxylase, an excess of the sodium-retaining steroid 11-desoxycorticosterone as well as of androgens occurs, and the patients have hypertension associated with androgenicity. The pathologic physiology is still essentially the same—the adrenals are

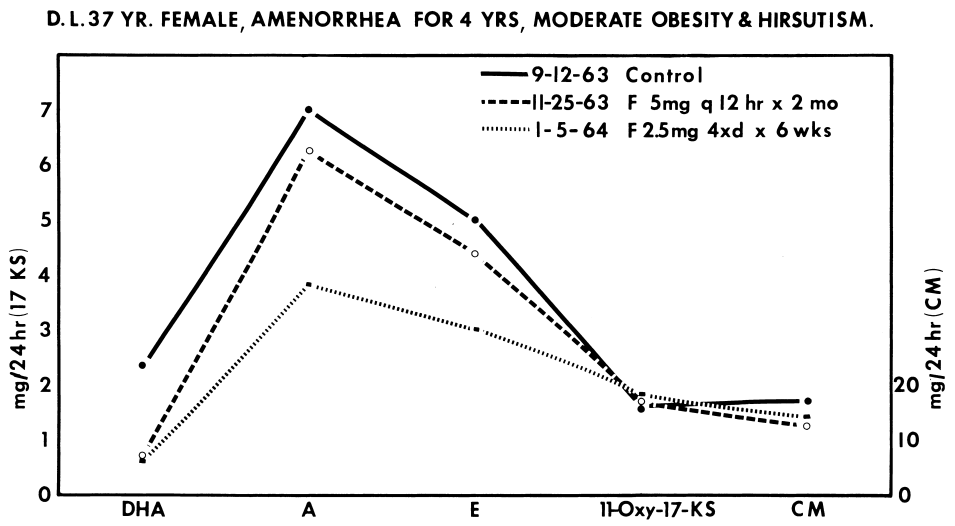

Figure 4. Effects of the same total daily dosage of cortisol administered in 2 divided doses and in 4 divided doses. F = cortisol, DHA = dehydroepiandrosterone, A = androsterone, E = etiocholanolone, 11-oxy-17-KS = 11-oxygenated-17-ketosteroids, and CM = cortisol metabolites. The values for fractions from each separate 24-hour urine collection are connected by lines to facilitate comparison. From William McK Jefferies, Glucocorticoids and Ovulation, in RB Greenblatt (Ed.), *Ovulation*. Copyright 1966, J.B. Lippincott Co., Philadelphia. Reprinted by permission.

being stimulated to work overtime to produce a sufficient supply of cortisol, and in the process they produce an excess of other steroids. Hence, the treatment is the same: administration of sufficient cortisol to restore normal levels of the other steroids. In patients with 11-beta-hydroxylase deficiency, treatment with cortisol not only counteracts the androgenicity but also restores blood pressure to normal, provided permanent damage to the kidneys has not occurred. These patients have an interesting combination of relative adrenal insufficiency with hypertension and emphasize that a low blood pressure is not essential for the diagnosis of relative adrenal insufficiency.

A patient who demonstrates the subtle aspects of diagnosing this type of congenital adrenal hyperplasia is described in Case 8.

Case 8

This forty-three-year-old male was referred because of recurrent hyperthyroidism. He had had high blood pressure as long as he could remember, but he did not know what treatment he had been given for this. He had not been taking any

medication for several months prior to his visit. He said he was a large baby at birth and that he had been very strong as a child. He remembered eating heartily when he was three years old, and he was unusually strong until age eighteen, when his strength seemed to leave him suddenly, about the time he had a tumor removed from his right breast. Symptoms of hyperthyroidism had developed at age thirty-seven; he took medication for this for two years with improvement.

A year before his referral, at age forty-two, he had a return of nervousness that he attributed to a vasectomy that had been performed four months previously. Six months later, he had influenza and was quite ill with complicating pneumonia. Subsequently, his symptoms of excessive nervousness and fatigue became worse. He had felt warm and had noted an increased pulse rate, but there had been no change in weight. Prior to the influenza attack, he said he had had no respiratory infection for at least ten years.

The patient denied having ever had any headaches, but his energy had frequently been poor. He was married and had three children. There was no family history of diabetes mellitus, but his mother had high blood pressure.

Physical examination revealed a height of 65½ inches, weight 152½ pounds, blood pressure 160–170/90–100, pulse 88 and regular. He was very tense and restless, with moderate hirsutism. There were no eye signs of hyperthyroidism and he had minimal tremor. The thyroid was soft, difficult to outline, approximately two-and-one-half times normal size. There was no lymphadenopathy. The remainder of his examination was not remarkable. White blood count was 5,900 with 76% neutrophils, 22% lymphs, 1% monocytes, and 1% eosinophils. Twenty-four hour I^{131} uptake over the thyroid was 29%; T^3 sponge uptake was 67% (normal 40–60%), and T^4 was 9.4 mcg% (normal 4.0–10.0). T^3 by RIA was 180 mcg% (normal 65–215). Plasma cortisol at 1:15 AM was 10.9µg%, a relatively low value for this time of day, but thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 27.9 µg%, consistent with normal adrenal responsiveness.

Because his history suggested the presence of excessive androgen at an early age plus asymptomatic hypertension for many years, a blood sample was drawn for plasma desoxycorticosterone (DOC). This was reported to be 355 ng%, with a normal range of 5–15. Repeat determinations obtained several weeks later were 275 and 349 ng%.

This patient therefore had not only symptoms suggestive of a mild recurrence of hyperthyroidism without laboratory confirmation but also congenital adrenal hyperplasia characterized by excessive production of androgen and DOC. A diagnosis of congenital adrenal hyperplasia associated with a deficiency of 11-beta-hydroxylase was therefore made. Cortisol, 5 mg four times daily, was prescribed, and his strength and sense of well-being improved impressively, but symptoms of hyperthyroidism became more pronounced; T^4 increased to 12.5 mcg% and T^3 by RIA to 250 ng/100 ml, so propylthiouracil, 50 mg four times daily, was added to his therapy. T^3 and T^4 and symptoms of hyperthyroidism returned to normal, but plasma DOC remained elevated until the dosage of cortisol was increased to 7.5 mg four times daily. Five months later, T^3 by RIA was 160 ng/100 ml, T^4 9.0 mcg%, and plasma DOC 6.8 ng/100 ml. Blood pressure decreased to 120–135/80–90. It was therefore

evident that he not only experienced symptomatic improvement on cortisol therapy but blood pressure also decreased to normal range. Propylthiouracil was discontinued after a year, and hyperthyroidism has remained in remission.

The recurrence of hyperthyroidism with a diffuse thyroid enlargement in this patient with congenital adrenal hyperplasia, and the apparent aggravation of symptoms and laboratory evidence of hyperthyroidism after the patient received cortisol, raise a question of the possible significance of adrenocortical function in patients developing hyperthyroidism. That Graves' disease, or hyperthyroidism due to diffuse goiter, has been demonstrated to be a manifestation of an autoimmune phenomenon associated with the production of an abnormal thyroid stimulator, and the apparent relationship between autoimmune phenomena and adrenocortical function, provide support for such speculation. In addition, evidence that physiologic dosages of cortisol may increase T_3 receptor function, as discussed in Chapter 10, further suggests a possible mechanism of the influence of cortisol upon thyroid function.

A deficiency of 11-beta-hydroxylase is thought to be a relatively rare cause of hypertension, but it should be considered in women with hypertension plus associated androgenic changes or elevated urinary 17-KS and in hypertensive men, especially in younger age groups. Perhaps it may be more common than is presently suspected. It is interesting to note than an earlier report[16] mentioned a blood pressure lowering effect of cortisone as well as a blood pressure elevating effect of ACTH in some hypertensives. The occurrence of partial 11- and 21-hydroxylase deficiencies in patients who develop hypertension, hirsutism, and menstrual disorders in late childhood or early adulthood[17,18,19] has been demonstrated and termed "acquired" adrenal hyperplasia, emphasizing the importance of careful studies in such cases. An interesting feature of hypertension associated with 11-beta-hydroxylase deficiency is that it may persist for years without complications such as renal damage. The ability to test for elevated levels of desoxycorticosterone in blood or urine should simplify the diagnosis of this curable form of hypertension.

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Chapter 5

GONADAL DYSFUNCTION AND INFERTILITY

The beneficial effects of physiologic dosages of cortisone acetate and cortisol in patients with congenital adrenal hyperplasia led to their being tried in women with ovarian dysfunction, hirsutism, and acne, since this combination of abnormalities occurred in both types of conditions. The dosages of glucocorticoids initially administered were relatively large, in the range of the full replacement dosages employed in congenital adrenal hyperplasia. Improvement occurred, but the possibility of adrenocortical suppression and impairment of resistance to stress from such doses was disturbing, so progressively smaller doses were tried, and we were pleased to find that impressive improvement occurred from physiologic dosages of 5 mg four times daily or even 2.5 mg four times daily, provided treatment was continued for a sufficient length of time.[1] It was therefore postulated that such cases might represent variants of the adrenogenital syndrome, viz., mild disorders of adrenal steroid metabolism characterized by excessive production of adrenal androgen and estrogen in sufficient quantities to interfere with ovarian function.

At that time, assessment of adrenal steroid production was limited clinically to measurements of urinary excretion of 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OHST), resulting in indirect estimates at best, since levels of urinary metabolites might be affected by steroid metabolism in the liver and peripheral tissues, by blood levels of steroid-binding proteins, or by renal function, as well as by changes in rate or pattern of steroid production by the adrenals.

Responses of urinary excretion of 17-KS and 17-OHST of these patients to a standard stimulus with ACTH were usually consistent with normal adrenal responsiveness, but when urinary 17-KS were fractionated, excretion of dehydroepiandrosterone (DHEA), androsterone (A), and etiocholanolone (E) frequently showed much greater variation than that of women with regular ovulatory cycles.[2]

Later, when plasma levels of cortisol, testosterone, DHEA-sulfate, estrogen, and FSH could be measured, it was found that some women with gonadal dysfunction that could be corrected by subreplacement dosages of cortisone acetate or cortisol had poor responsiveness to ACTH indicative of low adrenal reserve, some had elevated levels of free (or unbound) testosterone or of DHEA-sulfate, and some had elevated or low levels of estrogen and low or normal levels of FSH. Those with elevated plasma free testosterone had associated acne and hirsutism, but urinary 17-KS excretion might be within normal limits. On the other hand, some women with acne and/or hirsutism might have normal plasma testosterone with elevated urinary 17-ketosteroids, indicating the production of an excess of androgen other than testosterone, usually DHEA. Women with elevated levels of estrogen usually had metropathia hemorrhagica.

After subreplacement dosages of glucocorticoids were found to correct ovarian dysfunction in this type of patient, studies were undertaken to determine the effects of small doses of cortisone acetate on fluid and electrolyte excretion as well as urinary steroid levels.[3] It was found that small changes in urinary sodium and potassium excretion did occur but that these changes were corrected within eight days even though the steroid was continued (see Fig. 2). It was also noted that a new, stable level of urinary steroid excretion did not occur until approximately ten to fourteen days after these small doses were initiated. It was further found that these small doses did not interfere with the adrenals' ability to respond to a standard dose of ACTH[3] (Fig. 5).

The concept of a close functional relationship between the ovaries and the adrenals is not new. The steroid-forming tissues of the gonads and adrenal cortices have a common embryonic origin, and these glands share many enzymatic steps in the production of their steroid hormones. The changes in adrenocortical activity that occur at puberty and the menopause further suggest a close association between these two pairs of glands. The well-known effects of stress upon the function of both of these pairs of glands could be due to simultaneous independent effects or to a sequential effect wherein the effect of stress upon one pair of glands, e.g., the adrenals, in turn affected the function of the other pair of glands. Clinical observations that patients with disorders of adrenocortical function, such as adrenal insufficiency (Addison's disease), hyperfunction (Cushing's syndrome), or dysfunction (congenital adre-

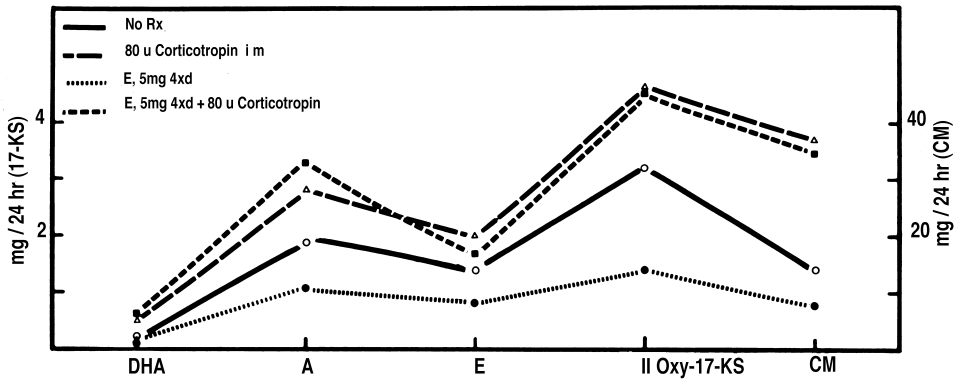

Figure 5. Effects of same dose of corticotropin (ACTH) administered to a 13 year old girl with probable rheumatoid arthritis upon urinary steroid fractions before treatment and while in a symptomatic remission on cortisone acetate (E), 5 mg four times daily (4 × d) (DHEA = dehydroepiandrosterone, A = androsterone, E = etiocholanolone, 11-oxy-17 KS = 11-oxygenated-17-ketosteroids, CM = cortisol metabolites). From William McK Jefferies, Low Dosage Glucocorticoid Therapy, *Archives of Internal Medicine, 119:*265–278. Copyright 1967, the American Medical Association. Reprinted by permission.

nal hyperplasia), had associated disorders of gonadal function were consistent with the concept of a close relationship between these glands. Furthermore, when cortisone was first tried in women with rheumatoid arthritis, interference with normal menstrual cycles was reported.[4,5]

In spite of such abundant suggestive evidence of a functional relationship between the gonads and adrenal cortices, this relationship has not been very intensively studied. Andrews[6] has summarized reports prior to 1976 relative to this relationship and pointed out the need for more work in this field. The work of Kitay and his associates[7,8] emphasizes the subtle nature but important potential of these relationships. They found that in castrated rats, estrogen replacement increases ACTH secretion and decreases adrenal responsiveness to ACTH, whereas androgen decreases ACTH and increases adrenal responsiveness to ACTH. They also reported that low doses of testosterone stimulate adrenal enzymatic and steroidogenic capacity, but large doses have inhibitory effects. Furthermore, testosterone may potentiate the action of ACTH.[9] The possible effects of adrenal progesterone upon gonadal function remain to be clarified.

Our observations in women with adrenal insufficiency reported in Chapter 4 also indicate the sensitive but potent interactions of these two

sets of glands. The occurrence of amenorrhea in these women, the restoration of normal menstrual cycles and fertility by administration of physiologic dosages of cortisone acetate or cortisol in cases of spontaneous deficiency, and the requirement for supplementary small doses of DHEA in the patient with total bilateral adrenalectomy exemplify this relationship.

Initially, treatment of ovarian dysfunction with small dosages of cortisone acetate or cortisol was restricted to patients with associated acne or hirsutism, but after observing the safety and beneficial effects of such therapy, it was decided to try similar dosages on patients who had ovarian dysfunction without hirsutism or acne. Many of these patients also experienced improvement in their clinical disorders.

Menstrual problems encountered included amenorrhea, either primary or secondary, but more often the latter, irregular menses, functional uterine bleeding, and luteal phase disorders. Women with ovarian dysfunction tend to have a high rate of infertility, and small doses of cortisone acetate or cortisol not only resulted in improvement of abnormal menstrual cycles but also in ability to conceive and to carry pregnancies normally to term. Effective dosages were as small as 2.5 mg every eight hours but usually were 2.5 or 5 mg four times daily.[10–13] Although these dosages do not impair resistance to stress, in fact they enhance this resistance, it is probably safer to give additional cortisol at delivery, especially if caesarian section is performed, because of recent evidence that autoimmune disorders may result from a defective response of the hypothalamus-pituitary-adrenal (HPA) axis to more severe stresses (see p. 99). Because the dosages are physiologic, they may be continued during lactation without harm to either the mother or her infant.

These findings were initially reported in 1958,[1] but meanwhile reports of harmful side effects of large doses of glucocorticoids were becoming so frequent that any dosage was viewed with alarm. By the time that I was able to report results on a significant series of cases,[14] patents had expired on cortisone acetate and cortisol, and there was no incentive for pharmaceutical houses to seek further clinical uses of these agents even though the results of this therapy were impressive. Over 80 percent of women with ovarian dysfunction not related to some other disorder such as pituitary insufficiency or primary ovarian deficiency experienced a restoration of normal menstrual cycles, and of those who had associated fertility problems, 62 percent conceived and carried their

pregnancies normally to term, provided they continued to take the medication throughout the pregnancy.

Meanwhile, clomiphene sulfate had been introduced as an agent to help stimulate ovulation and promote fertility in patients experiencing difficulty in conceiving. Clomiphene is not a natural hormone, but it is effective in some patients, and it had the protection of a patent to cause the pharmaceutical company marketing it to promote its sale enthusiastically. Because it does not correct the underlying hormone disorder but instead stimulates ovulation in a relatively artificial manner, a smaller percentage of patients conceive with clomiphene therapy than with small doses of cortisone acetate or cortisol, and of those who do conceive, a higher incidence of multiple births and of miscarriages occurs.[15,16]

Patients treated with physiologic dosages of cortisone acetate or cortisol, on the other hand, not only conceived, but they carried their pregnancies with an incidence of miscarriages no greater than that of the general population, provided the steroid was continued through the pregnancy.[14] In other words, small dosages of cortisone acetate or cortisol seemed to protect against miscarriage as well as improve conception rate. For these reasons, small doses of cortisone acetate or cortisol are preferable to clomiphene, and we have tried the latter only in patients who fail to respond to physiologic cortisone therapy. On occasion, a patient has conceived with clomiphene administration after low dosage glucocorticoid had failed, but numerous women have conceived on low dosage glucocorticoid therapy after having failed to conceive with clomiphene that had been prescribed prior to referral to me.

Most women who have androgenic changes such as acne and hirsutism associated with ovarian dysfunction have an increased excretion of urinary 17-KS or elevated levels of testosterone or DHEA-sulfate in the blood, and the adequacy of treatment is reflected by the return of such measurements to normal. Hence, initially it was postulated that the ovarian dysfunction was caused by an excess of androgen. Later when it was found that dysfunction could occur without any excess androgen and still be corrected by small doses of cortisone acetate or cortisol, it was concluded that an excessive production of estrogen by the adrenals, or at least under ACTH control, must be the cause of the disorder.[17,18] An excessive production of estrogen can often be demonstrated in patients with functional uterine bleeding, and the restoration of normal ovulatory cycles by small doses of glucocorticoids suggests that the

excessive estrogen either was being produced by the adrenals or was under ACTH control.

Two reports may be pertinent relative to the etiology of this type of hormonal disorder. Herrenkohl[19] has noted that prenatal stress of mother rats resulted in reduced fertility in their female offspring, with fewer conceptions, more spontaneous abortions and vaginal hemorrhages, longer pregnancies, lower birth weight, and fewer newborns likely to survive the neonatal period. Gupta et al.[20] reported that phenobarbital administration to pregnant rats also produced detrimental effects on reproductive function in their offspring, including delays in the onset of puberty, disorders in the estrous cycle, and infertility, associated with altered concentrations of sex steroids, gonadotrophic hormones, and estrogen receptors.

Other recent studies have brought to light another type of abnormality that can cause clinical disorders that might improve with physiologic dosages of glucocorticoid, namely, autoimmune phenomena. Because ovarian hormones as well as adrenocortical hormones are steroids, they do not stimulate the production of antibodies, but steroid hormone receptors are protein molecules and, hence, can stimulate antibodies that could interfere with normal estrogen effect. Such cases might have normal or elevated plasma estrogen levels, normal or slightly high plasma FSH, and amenorrhea or irregular menses. Breast development might also be poor. Ovarian dysfunction associated with severe insulin resistance has been described as the "Type A Syndrome,"[21] so it seems likely that ovarian dysfunction could occur as an autoimmune disorder without insulin resistance. If such occurs, the beneficial effect of glucocorticoids in autoimmune disorders, even in subreplacement dosages (Chapters 6, 7 and 8), might account for favorable therapeutic responses.

Once the disturbed ovarian function has been corrected, the remission may be maintained in some cases after the glucocorticoid has been discontinued, but most women seem to need to continue the treatment indefinitely to maintain normal ovarian function. We have not been able to follow a sufficient number of daughters of patients with ovarian dysfunction into adolescence to determine whether they can inherit this type of disorder, but there is considerable evidence from patient histories that this clinical problem does tend to be inherited.

It should be remembered that amenorrhea may be caused by other disorders such as hypopituitarism, prolactin-producing tumors of the

pituitary, hypothyroidism, and primary ovarian deficiency, as well as by congenital defects in genital development, and that irregular menses can result from relative ovarian deficiency, but the majority of women with irregular menses, secondary amenorrhea, functional uterine bleeding, and luteal phase disorders will benefit from low dosage glucocorticoid therapy, and associated infertility, if present, will often be corrected.[14]

In the field of ovarian dysfunction, some confusion has arisen in the use of the term Stein-Leventhal syndrome. This syndrome as originally described[22] included not only ovarian dysfunction and androgenic changes but also bilateral polycystic enlargement of the ovaries. It has been found to be associated with an abnormality of steroid metabolism in the ovaries, but in our experience, such patients usually require small doses of cortisone acetate or cortisol in addition to small doses of estrogen to have a restoration of normal menstrual cycles and fertility. This syndrome, therefore, results from a more severe degree of steroid abnormality than is encountered in the majority of women with ovarian dysfunction and androgenic changes, so it does not seem wise to apply the term Stein-Leventhal syndrome to the milder, more common disorder. The tendency to apply the term loosely to all types of ovarian dysfunction is, therefore, misleading, and the diagnosis should be limited to those women who have not only ovarian dysfunction but also bilaterally enlarged polycystic ovaries.

Several case histories demonstrate the promising potential and safety of low dosage glucocorticoid therapy in ovarian dysfunction.

Case 1

The patient was a seventeen-year-old female referred for primary amenorrhea. She had experienced slight breast development for several years but no spontaneous menses. Premarin, 1.25 mg daily for three weeks, plus Provera, 10 mg daily for the last five days, cyclically, for four months, had produced withdrawal flow but no subsequent menses. Her general health and energy had been good. She had no acne or hirsutism, and temperature tolerance was normal. She had no history of serious illness and no allergies. Her younger sister, age fifteen, had the menarche at age fourteen, and her cycles were regular but with a prolonged flow of nine days. The patient's paternal aunt had had a goiter removed, and grandparents on both sides had senile type of diabetes mellitus.

Physical examination revealed a pleasant, attractive girl with a clear complexion. Height was 67½ inches, weight 119½ pounds, blood pressure 90/60, pulse 76 and regular. She shaved her thighs but otherwise had no excessive hair growth.

The thyroid was at the upper limits of normal in size, with no lymphadenopathy. Breast development was poor, and there were no masses. The remainder of the examination was normal except for slightly hypoactive reflexes. T_3 sponge uptake was 36%, and T_4 was 7.3 mcg%. Plasma estrogen was 185 pg/ml (normal 45–200), and plasma FSH 11.7 mIU/ml (normal 15–30). Plasma cortisol at 1:30 AM was 11.3 mcg%, a somewhat low value for that time of day; 30 minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 27.7 mcg%, consistent with normal adrenal responsiveness.

The occurrence of high normal plasma estrogen and low plasma FSH in association with amenorrhea and subnormal breast development suggested either the production of abnormal estrogen, possibly under adrenal control, interfering with normal ovarian function, or some abnormality of estrogen receptors, possibly autoimmune in nature. Cortisol, 5 mg four times daily, was therefore started. She returned six weeks later reporting considerable improvement in energy and sense of well-being, and she commented on having had no respiratory infections or influenza although two brothers and her father developed flu during an epidemic that was in progress at that time. There had also been much influenza at her school.

No evidence of ovulation occurred on basal temperature charts, however, and no menses occurred, so after three months, the dosage of cortisol was increased to 7.5 mg four times daily. Within two weeks she had her first spontaneous menses. A month later T_3 sponge uptake was 51%, T_4 was 8.4 mcg%, and plasma estrogen was 49 pg/ml.

Although estrogen levels fluctuate during normal menstrual cycles, the decrease in plasma estrogen while the patient was taking cortisol and after she had spontaneous menses suggested that the cortisol had corrected either an excessive production of estrogen from some extra-ovarian source or an abnormality of estrogen receptors.

Because the patient's thyroid was still at the upper limit of normal in size, Euthroid, gr ½ twice daily was added to her therapy. Subsequently, basal temperature charts showed evidence of more regular ovulatory menstrual cycles, and breast development increased to normal. A repeat plasma estrogen determination was 73 pg/ml.

This case is an example of primary amenorrhea associated with a normal level of plasma estrogen and a low level of FSH. The poor breast development and lack of menses suggested that the estrogen was either not a normal type or that its physiologic effects were being blocked, and the relatively low baseline plasma cortisol suggested some adrenal disorder. She also had a slight nontoxic thyroid enlargement with a family history of goiter and diabetes mellitus, and her ovarian function did not show optimum improvement until suitable doses of thyroid medication were administered with the cortisol. At the time she was studied, measurement of T_3 by RIA was not available, but recently a similar case has

been encountered whose T_3 by RIA was low while T_3 sponge uptake and T_4 were normal. This patient also appeared to have a high resistance to common respiratory illness and influenza while taking physiologic dosages of cortisol in contrast to the resistance-impairing effects of large, pharmacologic dosages.

The patient in case 2 was also referred at the age of seventeen years, but she had secondary amenorrhea of eight months duration.

Case 2

The menarche had occurred at age ten, and cycles had been regular with intervals of twenty-eight to thirty days, menses lasting four days, until about eighteen months previously, when intervals increased up to two months and duration of flow decreased to two days. Menses stopped altogether eight months prior to the patient's referral. She had experienced acne since the menarche, treated since the previous summer with tetracycline, one tablet twice daily. She had also been receiving injections for allergic rhinitis and sinusitis for several years, but these injections had been discontinued at about the time of her last menstrual period. Her allergy symptoms had been worse in the spring before her visit. Thyroid enlargement had been noted intermittently since the previous summer. She had one sister, age sixteen, with regular cycles. Her maternal grandfather had diabetes and her father and paternal grandmother had hypertension.

Physical examination revealed moderate acne of the face and slightly increased hair growth on her trunk. The thyroid was not enlarged. Breast development was normal with no masses. Blood pressure was 100/75, pulse 92 and regular. Height was 64¾ inches, weight 117 pounds. Pelvic examination was normal, with no enlargement of the ovaries. Urinary 17-KS were 13.9 and 17-OHST 3.9 mg/24 hours.

The patient was given cortisol, 2.5 mg four times daily, and she returned two months later reporting that a spontaneous menstrual period lasting four days had occurred. She also reported significant improvement in her complexion, although she had discontinued tetracycline several weeks previously. Allergic symptoms had also improved. She was reluctant to continue to take the cortisol, however, because she had read reports of the hazardous potential of glucocorticoid therapy, and after she had been getting along well for several months, she discontinued it. Her cycles continued to be fairly regular, but she experienced exacerbation of her acne and allergies after the cortisol was stopped.

Conjugated estrogen (Premarin), 0.3 mg daily except during menses, was then tried. This produced impressive improvement in her acne, but her allergies seemed worse, so cortisol, 5 mg four times daily, was resumed. On this program she did quite well, with regular menstrual cycles, few allergic symptoms, and only occasional mild acne. Several years later when she read news reports regarding the possible harmful effects of Premarin, she discontinued it. Her cycles continued regular on the cortisol, and her complexion remained clear.

This patient is an example of a young woman with secondary amenorrhea and acne that responded to small doses of cortisol. Her acne also improved with a small dosage of Premarin, but this did not help her allergic symptoms, whereas cortisol had benefited her acne, her allergic symptoms, and her ovarian dysfunction. Her case also demonstrates how some patients with acne who have been treated with tetracycline can discontinue the tetracycline when they receive suitable dosages of cortisol. Her experience further emphasizes the need for the news media to report the value of safe dosages as well as the potential harm of excessive dosages of normal hormones. The tendency for the news media to dramatize the hazardous aspects of therapy with adrenocortical and ovarian hormones without pointing out the safety and need for physiologic dosages of these hormones in patients with certain types of hormone deficiency continues to be a serious problem.

Case 3 is an example of a type of ovarian dysfunction seen somewhat more frequently in recent years.

Case 3

This woman was referred at the age of twenty-two years because of secondary amenorrhea. The menarche had occurred at age twelve, with fairly regular cycles for approximately two years, but they then became irregular with intervals of twenty-one to sixty days, menses lasting five days with severe cramps. At age eighteen, she was given an oral contraceptive to regulate her cycles, and she also married during that year. The oral contraceptive was discontinued three years later, but she had no subsequent spontaneous menses. She had experienced increased hair growth since age thirteen or fourteen, but this had apparently diminished while she was taking the oral contraceptive. Two lumps had been noted in the right breast, and they had subsided after aspiration.

Physical examination revealed a height of 65½ inches, weight 152 pounds, blood pressure 90/70, pulse 88 and regular. There was moderately excessive hair growth on the face, trunk, and extremities. The thyroid was not enlarged. Breast development was normal with no masses. The clitoris was not enlarged. The remainder of her examination was not remarkable. Urinary 17-KS were 31.5 mg/24 hours. Blood FSH was 5.2 mIU/ml, total estrogens 19.6 pg/ml, and plasma testosterone was less than 30 ng/dl. Plasma cortisol at 11 AM was 9.3 mcg%; thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 42.3 mcg%. Urinary 17-KS after dexamethasone suppression decreased to 9.2 mg/24 hours.

On cortisol, 5 mg four times daily, urinary 17-KS decreased to 17.6 mg/24 hours, so the dosage was increased to 7.5 mg four times daily. She was also given a 1200 calorie diet on which she lost 17 pounds. On this program, she resumed having regular ovulatory cycles, and urinary 17-KS were 13 mg/24 hours. She did not wish to

become pregnant. In early 1976, she reported that her cycles were regular and that she had been the only one in her entire department at work who had not had influenza during that spring epidemic. Twelve others were quite sick and missed many days from work.

This type of disorder, in which ovarian function is apparently normal for several years, progressing to irregular menses and associated with androgenic changes, often progresses to amenorrhea spontaneously, but in this case the administration of an oral contraceptive for several years preceded the amenorrhea. The apparent aggravation of ovarian dysfunction after a prolonged course of an oral contraceptive has been observed in other patients and suggests that it may be advisable for patients with ovarian dysfunction to avoid use of oral contraceptives. The elevated urinary 17-KS excretion with normal plasma testosterone levels was consistent with the production of an excess of androgen other than testosterone. The responses to dexamethasone and to cortisol also indicate that the excess androgen was under ACTH control. The improvement in hair growth that apparently occurred while she was taking the oral contraceptive has been observed in other patients and suggests that the oral contraceptive can affect adrenocortical function as well as ovarian function. Finally, the failure of this patient to develop influenza during an epidemic that affected everyone else in her department at work was impressive and indicated that this therapy certainly was not impairing her resistance to infection.

Case number 4 is an example of the beneficial effect of cortisone or cortisol therapy in a patient with functional uterine bleeding.

Case 4

This sixteen-year-old girl was referred because of irregular menses and prolonged bleeding. The menarche had occurred at age fourteen, and cycles had always been irregular with intervals of two to six months, menses lasting eight days with occasional cramps. She had noted acne for about a year and also some increase in hair growth on her abdomen. For the previous six weeks, she had been spotting continuously. Her general health was good. She had a history of an appendectomy for a ruptured appendix at age nine, and there was a family history of goiter on both maternal and paternal sides.

Physical examination revealed an attractive young woman with mild increased hair growth in the periareolar and subumbilical areas. The thyroid was not enlarged; blood pressure was 90/60, pulse 72 and regular, height was 63 inches, weight 102½ pounds. Neither the clitoris nor the ovaries were enlarged. Urinary 17-KS

were 13.5 mg/24 hours. She was given progesterone, 5 mg by mouth daily for five days to produce an initial withdrawal flow, and Cortef, 5 mg four times daily. On this medication, she resumed regular ovulatory cycles, but she continued to complain of sensitivity to cold, and her energy did not return completely to normal. In August 1972, T_3 sponge uptake was 65% and T_4 was 4.0 mcg%. She was given a prescription for Euthroid, gr 1½ daily with impressive improvement in energy and less sensitivity to cold.

A year later, when she went to college, she discontinued the Euthroid and took the Cortef irregularly. If her menstrual period was late, she would take the Cortef until it developed. In January of her freshman year she had infectious mononucleosis, but she did not increase the dosage of Cortef. She stopped Cortef altogether in the spring of her sophomore year and during the subsequent year she developed progressive dysmenorrhea, with nausea and vomiting at the onset of her menses. When she returned for follow-up in the spring of her junior year, plasma cortisol at 2:15 PM was 11.6 µg%; thirty minutes after an I.M. injection of 25 units of Cortrosyn, plasma cortisol rose to 31.2 µg%. Plasma FSH was 6.0 and plasma estrogen was 125 pg/ml. T_3 sponge uptake was 63%, and T_4 was 6.9 mcg%. She was instructed to resume Cortef, 5 mg four times daily, and Euthroid, gr 1 daily, and she had a resumption of normal cycles and improvement in energy.

Features worthy of comment in this case include irregular menses from the menarche and flow lasting eight days. The occurrence of relatively prolonged flow with regular cycles may be a manifestation of mild hypothyroidism, but irregularity of the cycles is more frequently associated with a disorder of steroid metabolism. The development of metropathia is usually associated with an excessive production of estrogen, either from the adrenals or under ACTH control, that interferes with normal ovarian function and is corrected by physiologic dosages of cortisone acetate or cortisol. The history of a ruptured appendix at age nine is interesting because a number of other patients with ovarian dysfunction have given histories of having had a severe illness in childhood, suggesting that severe stress may predispose to this type of endocrine disorder. Administration of Provera is helpful in patients with metropathia to produce withdrawal flow because the pathologic physiology is an excessive stimulation of the endometrium by persistent estrogen production without the cyclic shedding that follows ovulation. The "medical D & C" produced by Provera therefore prevents persistent bleeding during the interval before the effects of corrective hormone therapy occur. A dosage of 5 mg Provera daily for five days seems to be preferable to 10 mg on the same schedule because it produces withdrawal flow yet is not as apt to inhibit ovulation as the larger dosage.

It is not unusual for the 5 mg dose to stimulate an ovulation, in which case menstruation does not occur until approximately fourteen days later, instead of the two to four day interval that occurs without ovulation.

Girls with metropathia frequently have mild hypothyroidism, and the response to Euthroid in this case was impressive, although T_3 sponge uptake and T_4 were within low normal range. The measurement of T_3 by RIA provides a means of detecting a decreased ability to convert T_4 to T_3 as a possible cause of thyroid deficiency in such cases at present, but this test was not available at the time this patient was studied. Of additional interest in this case is that ovarian dysfunction did not remain corrected after she discontinued medication, but it returned in somewhat milder form and persisted until Cortef and Euthroid were resumed.

Case 5 is an example of a girl with functional uterine bleeding that eventually progressed to amenorrhea.

Case 5

The patient was referred at age sixteen with a history of irregular prolonged uterine bleeding since the menarche at age twelve. Intervals between menses had been as long as six months and duration of flow as long as three weeks. A dilatation and curettage had been performed at age twelve, and subsequently she had been given an oral contraceptive for several months without benefit. Her last menstrual period had occurred ten months previously. Plasma FSH was 9.2 mIU/ml (normal 6–30), plasma total estrogens were 56 pg/ml (normal for preovulatory phase was 100–200; this was run by a different laboratory from that used for previous cases), T_3 sponge uptake was 53%, and T_4 was 6.7 mcg%, both well within normal limits. Plasma cortisol at 1:30 PM was 14.0; one hour after an I.M. injection of 25 units of ACTH, this rose to 37.3 mcg%.

She was given Cortef, 5 mg four times daily, and plasma estrogens increased to 175 pg/ml, but she failed to ovulate. Synthroid, 0.1 mg daily, was added, later increasing to 0.15 mg daily, but she did not ovulate until the dosage was increased to 0.2 mg daily. She is now having regular ovulatory cycles on Cortef, 5 mg four times daily, plus Synthroid, 0.2 mg daily.

This girl had metropathia from the menarche at age twelve. Such patients are often given an oral contraceptive in a cyclic fashion to produce regular withdrawal flow, but this type of therapy does not usually help the fundamental disorder, and in some cases it seems to aggravate it. Prior to the availability of oral contraceptives, these patients were sometimes treated with cyclic estrogen and progesterone in physiologic dosages, and this therapy occasionally seemed to stimulate ovulatory

cycles after it was withdrawn, but patients frequently relapsed to metropathia within a few months. In this case, the normal plasma FSH with low total estrogens suggested the presence of estrogens that were not being measured in the assay. Cortisol therapy resulted in an increase in plasma estrogen level, consistent with an abnormality in steroid metabolism, but ovulation did not occur until she also received thyroid in a sufficient dosage, even though T_3 sponge uptake and T_4 had been normal prior to therapy. Patients with metropathia frequently require physiologic dosages of thyroid medication as well as cortisol or cortisone acetate, suggesting an associated mild thyroid deficiency even though T_3 sponge uptake and T_4 may be within normal limits. As stated previously, T_3 by RIA is a more sensitive indicator of thyroid function, but this test was not available at the time this patient was studied.

Case 6 is an example of ovarian and thyroid dysfunction with infertility.

Case 6

This twenty-five-year-old female was referred because of a thyroid disorder, irregular menses, and infertility. The menarche had occurred at age eleven, and cycles had always been irregular with intervals of four to six weeks, menses lasting three to five days with cramps. She had experienced acne since the menarche, and hirsutism for the previous two years. She was married at age twenty, took an oral contraceptive from age twenty to age twenty-three, and had used no precautions for eighteen months prior to her visit. After stopping the oral contraceptive, she developed abdominal pain and had a laparotomy for a "pseudocyst" of the ovary. When she failed to conceive, she received a bilateral wedge resection for sclerocystic ovaries six months prior to her referral. Meanwhile, she had been given injections of a progestational agent to try to correct her ovarian function. After the wedge resection, she had two menses a month apart, then cycles became irregular again. Her energy had been poor for about five years, she was sensitive to cold and had a tendency to constipation. She had experienced frequent palpitations and tremor in the previous year. Her brother was married and had two children. Her mother had ovarian dysfunction and had had difficulty in conceiving.

Physical examination revealed a height of 67 inches, weight 137-1/2 pounds, blood pressure 124/80, pulse 96 and regular. There was mild acne of the chin and mild periareolar hair. The thyroid was two-and-one-half times normal size, rather firm, with no lymphadenopathy. Breasts were hypoplastic, but within lower limits of normal and contained no masses. Heart, lungs, and abdomen were normal except for laparotomy scars. Reflexes were equal and hyperactive. T_3 sponge uptake was 52%, T_4 was 6.2 mcg%, thyroid antibodies were negative, total estrogen was 47 pg/ml (normal 100–200), plasma cortisol at 4 PM was 14.0,

and thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 39.3 mcg%.

She was given Euthroid, gr 1 daily, and Cortef, 5 mg four times daily. A month later her thyroid had returned to normal size and her menstrual cycles became more regular with evidence of ovulation on the twelfth to fourteenth days of twenty-five to twenty-eight day cycles, but she failed to conceive.

Plasma estrogen was 133 pg/ml. Premarin, 0.3 mg daily except during menses, was added to her regimen and she conceived in the second cycle after this program was started. After conception, T_3 sponge uptake was 38%, and T_4 was 8.1 mcg%, but her thyroid began to enlarge, so the dosage of Euthroid was increased to gr 1 twice a day, Cortef being continued at 5 mg four times daily. She had a full term, normal delivery and nursed her baby for a month.

Because her tubes reportedly showed considerable scarring, her obstetrician advised another pregnancy as soon as possible. After delivery she resumed Cortef, 5 mg four times daily, and Euthroid, gr 1 daily. The Premarin had been discontinued as soon as her pregnancy had been diagnosed, and this was not resumed. She had two normal cycles and then conceived again. Euthroid was again increased to gr 1 twice daily, the continued at 5 mg four times daily, and she delivered a normal female infant by breech three weeks early. She did not nurse this baby, and menses resumed normally.

This patient was an example of the Stein-Leventhal syndrome with only transient improvement following wedge resection. She also had a nontoxic goiter with a normal T_3 sponge uptake and T_4. Plasma estrogen was low, but plasma FSH was in the low normal range, suggesting that she was either producing an estrogen that was not being measured or that pituitary function was mildly impaired. On a combination of Euthroid and Cortef, she resumed regular menstrual cycles, and her thyroid returned to normal size, but she failed to conceive until a small dose of estrogen was added. She had a second pregnancy on Cortef and Euthroid, but without estrogen. This case typifies the necessity of having not only ovarian but also adrenal and thyroid function normal before conception can occur.

Although the pathologic cause of the Stein-Leventhal syndrome (polycystic ovary syndrome) has not yet been completely clarified, a recent review by Ehrmann et al.[23] summarizes the present status of the problem. On the basis of our experience, it appears to be associated with abnormal function of the adrenals, the ovaries, and at least sometimes also the thyroid, and often may be corrected by administration of a proper combination of small, physiologic dosages of cortisol, estrogen and thyroid, as occurred in this case.

Case number 7 is that of a seventeen-year-old girl with metropathia associated with elevated plasma estrogen apparently related to emotional stress.

Case 7

This patient had the menarche at age eleven, and her cycles were regular with intervals of twenty-eight days, menses lasting four to five days. At age fifteen, she developed emotional problems, for which she was treated with Thorazine®. She then began to have frequent, prolonged menses with intervals of two to three weeks, flow lasting up to three weeks. She had been given an oral contraceptive for three months without benefit. She tended to tire easily and for several years had been sensitive to both heat and cold. She had mild premenstrual acne and in recent months had also noted increased hair growth on her upper lip. During the previous year, she had frequent sore throats, and a tonsillectomy had been recommended. During this year her weight increased from 115 pounds to 154 pounds in spite of attempts to diet. In the previous two weeks she had experienced frequent headaches. She drank four large glasses of cola daily and had been smoking one and a half packs of cigarettes daily for five years. One of her three sisters had metropathia, and her mother was reported to have high blood pressure.

Physical examination revealed a stocky female with mild acne of the chin and mild increased hair growth on her upper lip and trunk. Height was 63 inches, weight 154¼ pounds, blood pressure 120/70, pulse 92 and regular. The thyroid was not enlarged. Breast development was normal, with no masses. The remainder of her examination was not remarkable. T_3 sponge uptake was 40%, T_4 was 8.0 mcg%, and plasma FSH was 11.7 mIU/ml, all normal values. Plasma estrogen was 356 (normal 45–200) and plasma estradiol 282 pg/ml (normal 15–75). Plasma cortisol at 9 AM was 21.1, and thirty minutes after an I.M. injection of 25 units of Cortrosyn this rose to 33.1 mcg%.

These findings were consistent with low adrenal reserve with an excessive production of total estrogen and estradiol. Plasma FSH was normal, rather than low, as would be expected with elevated estrogen. She was given Provera, 5 mg daily for five days, to produce withdrawal flow, and Cortef, 5 mg four times daily, to correct the steroid disorder. She was also given instructions for a 1200-calorie reduction diet and to decrease her intake of caffeine and use of tobacco. She failed to lose weight, but on this program she resumed regular ovulatory cycles with intervals of twenty-six, twenty-seven, twenty-eight, and twenty-three days, respectively, the latter cycle being complicated by a strep throat. Plasma total estrogen and estradiol levels returned to normal, although she continued to take psychotropic medication.

The development of ovarian dysfunction at the time she had emotional problems is consistent with the known tendency for stress to cause ovarian dysfunction in women who have a predisposition to such disorders, but psychotropic drugs can also cause ovarian dysfunction, so the taking of Thorazine may have contributed to this disorder. The association of elevated levels of total estrogen and estradiol with a normal level of plasma FSH suggests the possibility of a partial receptor block for estrogen that was corrected by the small dosage of cortisol.

Case 8 is that of a twenty-four-year-old female who was born and raised in Europe, moved to the United States at age sixteen, was married at age twenty-one, had used no precautions and had no pregnancies.

Case 8

The menarche had occurred at age thirteen, and cycles had been regular with intervals of twenty-seven to twenty-nine days, menses lasting four days without cramps. She had no acne. Frequency of intercourse was adequate. General health and energy had been good. Her hands and feet would get cold easily. She had no allergies. Her mother had some difficulty conceiving but eventually had two full-term, normal deliveries. Her husband had fathered a child by a previous marriage. Family history was negative for endocrine disorder.

Physical examination revealed a rather tall, well-developed, well-nourished young woman with no acne. The thyroid was soft, at upper limits of normal in size. Breasts were clear. There were a few periareolar and subumbilical hairs. Heart, lungs, and abdomen were normal. There was no edema. T_3 sponge uptake was 39.5%, and T_4 was 9.8 µg%, both normal values. Urinary 17-KS were 17.5 mg/24 hours and 17-OHST 16.4 mg/24 hours. Plasma cortisol at 8 AM was 21.2 µg%; one hour after an I.M. injection of ACTH, this rose to 34.5 µg%, consistent with low adrenal reserve.

Because of the suggestive slight thyroid enlargement, she was initially given Euthroid, gr 1 daily for four months. During this time basal temperature charts showed ovulations in cycles lasting twenty-seven to thirty-six days with good exposure but no conception. Cortef, 5 mg four times daily, was then added. Basal temperature charts showed evidence of ovulation nine days after Cortef had been begun, and she conceived with that ovulation. Cortef and Euthroid were continued in the same dosage up to the time of delivery of an 8 pound, 15 ounce, full-term, normal infant male.

This case is an example of how a history of regular menses does not rule out a mild hormone disorder as a cause of infertility. The presence of a small, nontoxic goiter indicated the need for thyroid medication, but conception did not occur until cortisol was added.

In recent years quite sophisticated and expensive methods of studying and treating ovarian and testicular dysfunction have been introduced, but no other treatments have apparently achieved the success of physiologic dosages of cortisol and/or thyroid for either women or men suffering from infertility with no apparent physical or hormonal disorders. It would therefore seem advisable for such patients to consider therapeutic trials with small doses of these normal hormones before resorting to more expensive procedures.

REPEATED MISCARRIAGES

As noted previously, women who have difficulty conceiving also have a high incidence of miscarriages, but when the physiologic dosages of glucocorticoid that are administered to correct the mild disorder of steroid metabolism or possible autoimmune disorder that interferes with their conceiving are continued throughout the pregnancy, the incidence of miscarriages is not greater than that of women who have no difficulty conceiving. In other words, continuation of the physiologic dosages of cortisol during a pregnancy helps to protect against miscarriage in this type of disorder.

For women who have repeated miscarriages without any apparent abnormality of their menstrual cycles, the administration of suitable doses of thyroid medication sufficient to bring the plasma thyroxine level above 8.0 mcg% is often beneficial in protecting the pregnancy.[18,24] Some women require both small dosages of cortisol and supplementary thyroid medication to prevent miscarriages.

Women who have difficulty conceiving should therefore have plasma thyroxine levels checked after conception, and if they do not rise above 8 mcg% within a month, the administration of sufficient thyroid medication to bring the level above 8 mcg% may help to protect against miscarriage. Because an occasional patient becomes resistant to extracts of animal thyroid glands, I prefer to prescribe synthetic preparations of sodium-L-thyroxine or sodium-L-thyroxine plus triiodothyronine for these patients. Daily dosages equivalent to one or two grains of additional thyroid medication are sufficient in most cases.

A woman who has corrected her difficulty in conceiving by taking small doses of cortisol should continue this medication through pregnancy up to the time of delivery. These small, physiologic dosages do

not harm the mother or her baby, and they seem to be necessary, in at least some cases, to enable the mother to maintain a normal pregnancy. As mentioned earlier (see page 68), because they do not impair resistance to stress, there is apparently no need to administer additional cortisol at the time of delivery, but because of recent evidence that autoimmune disorders may result from defective HPA responses to more severe stresses (see Chapters 6 and 8), it is probably safer to administer supplemental cortisol at the time of delivery, especially if Caesarian section is necessary or if the mother had previous evidence of adrenal insufficiency. In such cases, the administration of 50 mg Solu-Cortef intramuscularly every eight hours during labor or 100 mg intramuscularly one hour prior to caesarean section, followed by 50 mg every eight hours for twenty-four hours, then 25 mg intramuscularly every eight hours until oral medication can be resumed seems to protect against relative adrenal insufficiency without causing any harm to either the mother or her baby. After spontaneous vaginal delivery, the steroid can be resumed in the same maintenance dosage that had been taken during pregnancy as soon as the mother is able to take oral medication, and it may be continued through nursing without harm to the mother or her baby.

When thyroid medication is given to protect against miscarriage, it should be continued up to delivery, but after delivery, the dosage of thyroid should be reduced to the pre-pregnancy level. A woman not only needs but is also more tolerant of larger dosages of thyroid during a pregnancy, but if these larger dosages are continued into the postpartum period, symptoms of hyperthyroidism may develop.

The pathologic physiology of repeated miscarriages is not fully understood. After a woman becomes pregnant, her T_3 sponge uptake normally decreases and serum T_4 increases, reflecting the increase in thyroxine-binding globulin that occurs with increased estrogen activity, and patients with repeated miscarriages frequently fail to show these changes. One could postulate that the problem results from an inadequate production of estrogen, but the administration of estrogen to such patients does not seem to help to protect the pregnancy, and there are reports that some types of estrogen administration during pregnancy may be harmful. These seem to apply primarily to artificial estrogens such as diethylstilbestrol, but until this question is clarified, it is considered inadvisable to administer estrogen during pregnancy.

Evidence that placental synthesis of estrogen is closely linked to the supply of circulating dehydroepiandrosterone sulfate and hence to adrenocortical activity may be pertinent,[25] but the effect of cortisol or thyroid hormone administration upon DHEA-sulfate levels in women with repeated miscarriages has not been reported.

An excessive production of prostaglandins can cause miscarriage, but I have not seen any report that women with repeated miscarriages produce excessive amounts of prostaglandins, nor have I seen any report that administration of thyroid hormone or glucocorticoids affects prostaglandin production. It is possible that the protection against hypoglycemia provided by glucocorticoids may contribute to their protective effect. It is also possible that an abnormality of estrogen receptor function may be at fault.

It seems likely that some miscarriages, especially those that occur in the first trimester of pregnancy, may be related to the necessity for a mother to have a change in her immune system in order for her body to tolerate the fetus, which otherwise might be treated as a foreign body. Hence, further studies of this relationship should be helpful. It is apparent that changes in thyroid and adrenocortical function as well as in pituitary and ovarian function are necessary for a normal pregnancy, and this is probably the reason the three tropic hormones—thyrotropic, adrenocorticotropic and gonadoptopic—are all produced by the pituitary gland.

One might be concerned that protection of pregnancies under such circumstances might cause patients to carry abnormal fetuses to term, but in our experience this has not occurred. We have been able to obtain information on a total of 209 babies that have been borne by women who have taken physiologic dosages of cortisone acetate or cortisol through their pregnancies. These have included ninety boys, ninety-five girls, and twenty-four babies whose sex was not reported to us. Caesarean section was performed in twenty-seven instances on twenty-one patients, twice with each of three mothers and three times with one mother. Two sets of twins occurred. Only six of these 209 babies were reported to have congenital abnormalities; three had mild defects that were only temporary or easily corrected, whereas three had more serious disorders, including one Down's syndrome, one dislocated hip, and one infant with multiple congenital defects that died six hours after birth. This was the only fatality in the 209 infants. This incidence of congenital defects in

six of 209 babies is 2.9 percent, the same as the incidence of congenital malformations in live births in the general population.

Case 9 is an example of a woman with repeated miscarriages and no other apparent evidence of endocrine disorder who was helped by cortisone therapy.

Case 9

This young woman was referred to me in 1959, at age twenty-five, because of repeated miscarriages. She had reached the menarche at age sixteen, and cycles were regular at thirty-day intervals, menses lasted five days without cramps. She had been married two years previously. During her first pregnancy, she started spotting in her sixth week, was given some injections and some tablets (she could not identify these), but had a D & C for missed abortion in her fourth month. In her second pregnancy, she again started spotting at her sixth week, was given some tablets but miscarried at eight weeks. In her third pregnancy, she started spotting and miscarried at six weeks gestation. During this pregnancy she took no medication. Her energy was poor, and she was sensitive to cold. Most women notice an increased sensation of warmth and sensitivity to heat during a normal pregnancy, but she had noted no change in temperature tolerance during her pregnancies. Her mother had difficulty becoming pregnant, finally conceiving the patient after eight years, and she had no subsequent pregnancies. Her father had diabetes mellitus of recent onset.

Physical examination was within normal limits with no enlargement of the thyroid gland. PBI was 5.8 mcg%, and I^{131} uptake was 31% in twenty-four hours, both normal values. Response to TSH stimulation was normal. Urinary 17-KS were 10.4 mg/24 hours, also normal. Her basal temperature chart showed evidence of ovulation on the fourteenth day of thirty-day cycles. On sodium-L-thyroxine, 0.1 mg daily, her energy improved somewhat, and with the addition of cortisone acetate, 2.5 mg four times daily, her energy increased further. She then conceived again; a month after conception PBI was 6.8 mcg%, so the dosage of Synthroid was increased to 0.2 mg daily. She had slight spotting just before the dosage was increased, but it subsided after she stayed off her feet for two days. A month later PBI was 10.3 mcg%, and she carried her pregnancy to term without further problems, having a caesarean section. After delivery the cortisone was discontinued and thyroxine dosage decreased to 0.1 mg daily. She nursed her baby for six weeks, and menses resumed spontaneously three months postpartum. She conceived again eight months after her first delivery, this time while taking only thyroxine, 0.1 mg daily. Her dosage was increased to 0.2 mg daily three weeks after conception. She began spotting at that time, and this continued for about two weeks, then stopped. At seven weeks gestation, PBI was 7.6 mcg%. Spotting resumed in her eighth week, and she miscarried shortly thereafter.

Four months later menses had resumed normally, but there was evidence of chronic cystic mastitis. Cortisone acetate, 2.5 mg four times daily, was resumed in

addition to the thyroxine, 0.1 mg daily, and the patient reported impressive improvement in her energy; examination revealed the cystic mastitis had cleared. She conceived again shortly afterwards. Thyroxine was increased to 0.2 mg daily and cortisone acetate continued at 2.5 mg four times daily throughout her pregnancy, which was normal, ending in a full-term caesarean section. After delivery, she resumed cortisone acetate, 2.5 mg four times daily, and continued thyroxine, 0.1 mg daily, because she said she felt much better while taking these medications.

An ACTH test performed six months after her second delivery revealed baseline urinary 17-KS of 7.5 mg/24 hours and cortisol metabolites of 10.1 mg/24 hours. After 80 units of ACTH gel intramuscularly, urinary 17-KS increased to 8.6 and cortisol metabolites to 32.3 mg/24 hours.

The patient did not desire further pregnancies, so she had a tubal ligation. Thyroid medication was discontinued at age thirty-seven without apparent symptomatic change. An ACTH test at age thirty-seven, while she was taking cortisone acetate, 2.5 mg four times daily, revealed a baseline plasma cortisol of 17.1 mcg% at 9 AM; one hour after an I.M. injection of 25 units of ACTH this rose to 40.6 mcg%, consistent with normal adrenal responsiveness. She was therefore advised to try stopping the cortisone acetate, and four months later a repeat ACTH test revealed a baseline plasma cortisol at 9:15 AM of 30.5 mcg%; one hour after an I.M. injection of 25 units of ACTH, this rose to 71.2 mcg%. She has continued to feel well for the subsequent seven years.

This case demonstrated several interesting points. After having had three miscarriages in the first trimester, the patient had a full-term normal pregnancy on a combination of sodium-L-thyroxine and cortisone acetate, the latter in a dosage of only 2.5 mg four times daily. Subsequently, on thyroxine alone, she miscarried again. It is interesting to note that her serum PBI was 10.3 mcg% while taking thyroxine, 0.2 mg daily, during the pregnancy that she carried to term, and that it was only 7.6 mcg% while taking the same dosage of thyroxine during the pregnancy that miscarried. This suggests that the small dosage of cortisone acetate had in some way helped to increase the PBI level during pregnancy. She subsequently had another full-term normal pregnancy when cortisone acetate was given with the thyroxine in the same dosage as in the first pregnancy.

After having taken these normal hormones in small dosages for over twenty years, they were discontinued without any return of chronic fatigue, which had been the only subjective symptom that had responded to the therapy. It is therefore evident that prolonged treatment did not cause the patient to become dependent upon these medications but rather seemed to help enable her to continue to feel better after she stopped them.

TESTICULAR DYSFUNCTION

It is logical to assume that if mild adrenal dysfunction can produce disorders of ovarian function in women, it can produce disorders of testicular function in men because an excess of androgen or estrogen can impair normal spermatogenesis. Small doses of cortisone acetate or cortisol have therefore been administered to men with oligospermia, and an impressive number (about 50%) have had a significant rise in sperm count with this therapy.[26] Because normal human spermatozoa require about two months to mature, treatment should be continued for at least three months to determine whether it is being helpful. Some men with oligospermia may have elevated urinary 17-KS excretion, but most have a normal or relatively low excretion of these steroids. Some have elevated levels of plasma estrogen that can be suppressed to normal with small doses of cortisol, and some have mild gynecomastia. The dosages of cortisone acetate or cortisol are similar to those used for ovarian dysfunction. A possible reason that men have a lower percentage of response to this type of therapy is my impression that they sometimes do not seem to have as great an incentive to follow a detailed therapeutic program for fertility as carefully as their wives do, and this type of therapy must be followed meticulously to be maximally effective.

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Chapter 6

PHYSIOLOGIC DOSAGES IN RHEUMATOID ARTHRITIS: A RELATIONSHIP TO AUTOIMMUNITY AND TO MILD ADRENOCORTICAL DEFICIENCY

The antiarthritic effects of large doses of glucocorticoids are well-known. As has been mentioned previously, arthritis was the first pathologic disorder other than adrenal insufficiency for which glucocorticoid therapy was administered clinically, and because of the type of preparation and schedule of administration, the early dosages were much larger than what was later found to be a physiologic replacement dosage. When undesirable and hazardous side effects were encountered with such large dosages, it was assumed that any dosage would be dangerous. There has, therefore, been a tendency to avoid glucocorticoid therapy in arthritic conditions except as a last resort and then to discontinue it as soon as possible.

The evidence that cortisone acetate or cortisol can be administered in safe dosages that may be taken indefinitely without harmful side effects by patients with ovarian dysfunction raised the question of whether such safe dosages might have a place in the treatment of rheumatoid arthritis. An interesting report of one of the early patients with rheumatoid arthritis treated with cortisone acetate[1] implies that after initial dosages of 50 mg intramuscularly twice daily he was satisfactorily maintained on oral dosages of 50 mg and later 35 mg per day. The schedule of administration was not mentioned.

Thirty-six years ago, I reported the beneficial effects of *physiologic* dosages of cortisone acetate or cortisol on two patients with rheumatoid arthritis, with evidence that patients with rheumatoid arthritis seemed to have lower excretion of dehydroepiandrosterone in their urine and, hence, might have a mild abnormality of steroid metabolism.[2]

A review of the literature fails to reveal any attempts by others to confirm these observations or even any comment on them. The benefit of

low dosage glucocorticoid therapy in menopausal arthritis is exemplified in Case 6 in Chapter 4, and patients with other nonspecific types of arthritis have reported impressive improvement in arthritic symptoms when this treatment was administered for associated problems.

As an endocrinologist, I have not encountered many patients with rheumatoid arthritis, but three additional patients with this diagnosis were seen in the 1970s, and their responses to physiologic dosages of cortisone acetate or cortisol were also encouraging.

Case 1

The patient was a female, referred at age forty-six because of hypothyroidism associated with a goiter. Thyroid antibodies were present at a titer of 1:250, consistent with chronic thyroiditis, and she responded nicely to Euthroid, gr 1½ daily, plus cortisol, 5 mg four times daily. She also had a history of rheumatoid arthritis of twenty-five years duration, and when she was given the cortisol for her thyroiditis, she reported significant improvement in symptoms of the rheumatoid arthritis. This improvement continued for over five years, during which time cortisol was maintained at the same dosage except during respiratory infections, when it was temporarily doubled.

The coincidence of two autoimmune disorders, chronic thyroiditis and rheumatoid arthritis, in this patient was interesting and suggests some possible relationship. That low dosage glucocorticoid therapy administered for the thyroiditis also helped the arthritis strengthens this suspicion.

Case 2

The second patient was a female referred at the age of thirty-eight years because of irregular menses and occasional episodes of prolonged bleeding after her third and last pregnancy eight years previously. Four years prior to her referral, after a severe emotional upset, she developed pain and swelling in her fingers, ankles, and hips that was diagnosed as rheumatoid arthritis. Arthritic symptoms persisted until she was given cortisol, 5 mg four times daily, for the menstrual disorder. They then improved impressively, with disappearance of joint swelling and only occasional mild pain. Her ovarian dysfunction required a combination of cortisol, 5 mg four times daily, Euthroid, gr 1 daily, and Premarin, 0.3 mg daily except during menses, for optimum benefit and resumption of ovulatory cycles, and on this therapy her arthritis remained in remission for the three years that I was able to follow her.

Case 3

The patient was a man with rheumatoid arthritis referred because of difficulty controlling his arthritic symptoms with glucocorticoid therapy. He was fifty-three

years old and had had moderately severe rheumatoid arthritis for approximately twenty years, with a history of onset at the time of much stress at work. He had received gold injections but developed a reaction to these, so three years prior to his referral he had been started on "cortisone" injections at intervals of three to four weeks. In addition to the injections, he had been given prednisolone, 5 mg three times daily (equivalent to cortisol, 20 mg three times daily). Six months before his referral, injections had been discontinued and prednisolone dosage had been decreased to 5 mg twice daily. Motrin®, 400 mg four times daily, and Plaquenil®, 200 mg daily, had been added to his therapeutic program. His energy had been poor, and he had been sensitive to cold.

Physical examination revealed a thin male, with a height of 72 inches, weight of 149¾ pounds, and swollen, painful knees and ankles, who walked with difficulty using a cane. T_3 sponge uptake and T_4 were normal. After no prednisolone for over twenty-four hours, plasma cortisol at 8:45 AM was 11.2 μg%; after ACTH, this rose to 21.2 μg%.

It was therefore evident that he had maintained some adrenal responsiveness in spite of his glucocorticoid therapy, but the baseline plasma cortisol was low for the time of day at which it was drawn, and the response to ACTH was borderline. He had also been taking high potency vitamin and mineral supplements as well as "soya lecithin capsules," kelp, and large doses of Vitamin E. They were all tapered and discontinued except for a single supplementary multivitamin capsule daily. Prednisolone was discontinued, and cortisol, 7.5 mg four times daily, was given in its place. Motrin was continued.

During the subsequent two and one-half years, he slowly improved, his arthritis becoming much better with only mild persistent discomfort and slight swelling of his ankles. He gained 25 pounds and was able to walk more comfortably. At times of respiratory infections and also at times of urinary tract infections, the dosage of cortisol was temporarily increased, but after recovery it was returned to 7.5 mg four times daily. Urinary infections were related to urologic problems, and these were treated by a urologist.

These three cases were not dramatic, but they suggested a potential for physiologic dosages of glucocorticoids in rheumatoid arthritis, and the known safety of this type of therapy seemed to warrant its trial more extensively.

Another patient who demonstrated impressive benefit in symptoms of arthritis with a decrease in an elevated sedimentation rate to normal is Case 4.

Case 4

This patient was referred to me at the age of thirty-two years because of repeated miscarriages. The menarche had occurred at age twelve, with regular menses every twenty-eight days, lasting four to five days. She had some acne, worse premen-

strually, but no excessive hair growth. She was married at age twenty-two and had a full-term normal delivery two years later. Subsequently she had five successive miscarriages in a period of four years, all occurring at about the third month of gestation. She had been given estrogen and injections, probably progesterone, but no thyroid medication.

For the previous three or four years, she had experienced intermittent discomfort in her legs and knees, worse after exercise, with occasional swelling and tenderness of the joints. She had also tended to tire easily and had little energy. She had experienced frequent respiratory infections all of her life. Some increase in pigmentation at the sides of her forehead and in some small scars on her extremities had been noted during the previous few months. Eczema had been present in childhood, and "growing pains" had occurred at age six. Her health had otherwise been good. She had no brothers or sisters. Her father had mild diabetes mellitus.

Physical examination revealed a slender but normally developed thirty-two year old female with normal skin texture. There was slight brownish pigmentation at the sides of the forehead and in the antecubital fossae. She had mild acne but no excessive hair growth. The thyroid was slightly enlarged, approximately one-and-one-half times normal size, diffuse, nontender, but slightly irregular. Breast development was normal with no masses. Height was 62 inches, weight was 103½ pounds with shoes, pulse 72 and regular, blood pressure 115/70. A soft systolic murmur was present at the cardiac apex. Knee joints were not enlarged or tender. A TSH test was normal, with normal baseline PBI and I^{131} uptake and normal response to TSH stimulation. Urinary 17-ketosteroids were 6.5 mg/24 hours, and cortisol metabolites (similar to 17-OHST) were 6.9 mg/24 hours, both within low normal range. After 80 units of Acthar® Gel I.M., the 17-KS increased to 13.1 and cortisol metabolites to 36.5 mg/24 hours, consistent with normal adrenal responsiveness. Erythrocyte sedimentation rate was 30 mm/hour. Fractionation of urinary 17-KS revealed a low DHEA, a finding that had been observed in several patients with rheumatoid arthritis. She was given prescriptions for Synthroid, 0.1 mg daily, and cortisone acetate, 2.5 mg four times daily.

On this therapy she reported marked symptomatic improvement with rare joint discomfort. Her thyroid was still slightly enlarged, so the Synthroid dosage was increased to 0.15 mg daily. Her sedimentation rate decreased to 10 mm/hour. On several occasions when she discontinued the cortisone, joint pains and swelling returned, then subsided when medication was resumed.

After having been on this program for two years, she decided to try another pregnancy. After conception, the dosage of Synthroid was increased to 0.3 mg daily, the dosage of cortisone being continued at 2.5 mg four times daily throughout her pregnancy, which was uneventful and went to term with a normal delivery of a baby boy. She decided not to nurse her infant, and she felt so well that she took the cortisone quite irregularly for several months. Arthritic symptoms again returned, so she resumed the dosage of 2.5 mg four times daily with relief. After delivery, the dosage of Synthroid was returned to 0.15 mg daily.

Six months later arthritic symptoms returned while she was taking 2.5 mg four

times daily. Erythrocyte sedimentation rate was normal (5 mm/hour). The dosage of cortisone acetate was increased to 5 mg every eight hours with slight improvement, but joint pains and swelling persisted. The dosage was therefore increased to 5 mg four times daily. On this dosage, arthritic symptoms subsided and she felt quite well.

After four months, the dosage was decreased to 5 mg every eight hours because of a tendency to nocturia, and she continued to feel well.

Two years later she had another pregnancy, during which she took Synthroid, 0.2 mg daily, and cortisone acetate, 5 mg every eight hours, and she had a full-term, normal delivery. She did not nurse this baby either, and the dosage of Synthroid was decreased to 0.1 mg daily postpartum.

It was therefore evident that treatment with small doses of cortisone acetate and thyroxin enabled her to carry two pregnancies to term after having had five successive miscarriages. Her arthritic symptoms also seemed to be quite sensitive to the dosage of cortisone, being affected by very slight changes in dosage. Although her arthritis was not as severe as that of the previous three patients, the elevated sedimentation rate, joint swelling, and tendency to relapse whenever the dosage of cortisone was decreased suggested that it could be classified as rheumatoid arthritis.

Observations on one of the patients summarized in our report of 1967 [2] are of special interest because they suggest a possibility for preventing progression of rheumatoid arthritis if physiologic dosages of cortisone or cortisol are initiated early in the course of the disease. For that reason they will be briefly reviewed here.

Case 5

This patient developed migratory pains in the hips, elbows, metatarsal, and temporomandibular joints at age thirteen shortly after the menarche. After she had been unable to attend school for over a month because of these pains, intensive studies in the hospital resulted in a diagnosis of "probable rheumatoid arthritis," according to the criteria of the American Rheumatism Association.[3] The administration of cortisone acetate, 5 mg four times daily, resulted in complete relief of pain and swelling in approximately two weeks, and she was able to return to school.

A month later the dosage was reduced to 2.5 mg four times daily, and she remained asymptomatic for four months. A recurrence of pain and swelling in the joints then developed, so the dosage was returned to 5 mg four times daily. Subsequently, the dosage was decreased to 2.5 mg four times daily twice, but on both occasions joint pain and swelling recurred, once after a three-month interval and the second time after only a two-week interval, so she returned to 5 mg four times daily, a dosage upon which she remained asymptomatic. The menses, which had occurred at intervals of three to five weeks since the menarche, became regular at four-week

intervals after cortisone therapy was started. Steroid studies revealed no evidence of a summation effect of the exogenously administered cortisone, nor was there evidence that the plasma cortisol exceeded the normal range at any time with this therapy, even when it was checked one hour after a morning dose, the interval at which the maximum rise in plasma cortisol levels would be expected.

Six months after cortisone therapy had been started a small, nontoxic enlargement of the thyroid gland was noted. The administration of triiodothyronine, 25 mcg daily, resulted in return of the thyroid gland to normal size.

The patient was married at age nineteen and had normal pregnancies at age twenty and twenty-two, cortisone and triiodothyronine therapy being continued through both. Her arthritis remained in remission when cortisone dosage was maintained at 5 mg four times daily. At age 22 latex fixation was positive, but erythrocyte sedimentation rate was normal (8 mm/hour, corrected). At age 24, her steroid therapy was changed to cortisol, 2.5 mg four times daily. She was asymptomatic on this dosage for several months, but intermittent arthritis symptoms again returned, so the dosage was increased to 5 mg four times daily and symptoms again cleared. At age 27 sedimentation rate and SMAC were again normal, and an ACTH test revealed a baseline plasma cortisol at 9 AM of 28 µg/dl, rising to 35 µg/dl after Cortrosyn, consistent with low adrenal reserve.

This raised a question whether low adrenal reserve had been present since the onset of symptoms at age thirteen, or whether it had developed later. Observations in other patients indicate that prolonged administration of subreplacement dosages of cortisone acetate or cortisol does not impair adrenal response, so it is unlikely that her treatment would have caused this. The response of urinary cortisol metabolites to ACTH at age thirteen was apparently normal, but this is a less sensitive measure of cortisol production. Hence, we are unable to answer this question definitely, but it seems possible that low adrenal reserve had been present since the onset of her illness.

This patient was followed for fourteen years, from age thirteen to twenty-seven, during which she continued low dosage glucocorticoid therapy, married, and had two normal pregnancies. While she took cortisone acetate or cortisol in a dosage of 5 mg four times daily, her arthritis remained in remission, but whenever the dosage was reduced to 2.5 mg four times daily, symptoms eventually returned. Although the course of rheumatoid arthritis in young persons varies greatly,[4] the evidence that her arthritis relapsed whenever the dosage of cortisone was reduced suggests that the dosage of 5 mg cortisone acetate four times daily was preventing progression of her disease.

Many physicians treating rheumatoid arthritis have encountered pa-

tients whose symptoms can be maintained in a satisfactory remission on 15 or 20 mg of cortisone acetate daily, whereas withdrawal of the steroid is followed by recurrence or exacerbation. In several reviews of steroid therapy in rheumatoid arthritis, maintenance doses in this range are recommended, especially in women with cases of only moderate severity.[5–8]

The possibility that these dosages might act in any way other than as a summation effect has received little attention, however, and it has usually been implied that larger doses were necessary, at least initially. Therapeutic effectiveness of comparable small doses of prednisone (5 mg or less daily)[9,10] or dexamethasone (0.75 mg or less daily)[11] have been reported, but administration of the normal hormone, cortisol, in these physiologic dosages that have been demonstrated to be safe, seems preferable.

It therefore appears that therapeutic trials in a larger series of cases with initial doses of cortisol in this range for at least fourteen days before considering an increase are warranted, as are further studies to determine the nature of the antirheumatic effects. These recommendations were made in 1967,[2] but they still apply today.

The evidence that small, physiologic dosages of cortisone acetate or cortisol could benefit arthritis raised questions regarding the mechanism of antirheumatic effects. For many years, it was assumed that such effects depended upon production of an excess of steroid in the body, yet several observations suggested that this assumption might be incorrect.

For example, if the antirheumatic effect were primarily due to a summation effect, the greatest improvement should occur during the first two weeks of treatment, with a subsequent tendency to relapse. Instead, clinical experience has indicated that maximum beneficial effects do not occur until approximately two weeks after treatment is started, and they persist while the steroid is continued and for variable lengths of time after its withdrawal. The delay in attainment of maximum antirheumatic effect coincides to some extent with the time required for the body to adjust to exogenous steroid and raises the question whether some aspect of the adjustment might be responsible for this effect. Boland and Headley,[12] early in their experience with cortisone therapy of rheumatoid arthritis, noted that maximum overall improvement usually occurred two or three weeks after treatment was started and was "more frequently noted at or near the end of the gradual dose reduction." The similarity of time interval with that observed with low dosage therapy is interest-

ing and suggests that, even with larger doses, antirheumatic effect probably depends upon some factor other than hypercortisolism.

Although the beneficial effect of low dosage glucocorticoid therapy in arthritis might be related to its beneficial effect on autoimmune disorders, the mechanism of such beneficial effect remained to be explained. The possibility that an obscure abnormality of steroid metabolism contributes in some manner must be considered. Although relative deficiencies of excretion of DHEA are not pathognomonic of rheumatoid arthritis, nevertheless our finding that all five cases of this disease studied had similar abnormalities was impressive. Of further interest in this regard was a report[13] that women destined to develop rheumatoid arthritis have subnormal fertility and a reduced menstrual span. It was speculated that the lowered fertility and the arthritis, both of which might improve with low dosage glucocorticoid therapy, might be related to some underlying abnormality of steroid metabolism, possibly related to autoimmune factors.

Further evidence pointing to this possibility was the remission in rheumatoid arthritis that characteristically occurs during pregnancy. Although it has been generally assumed that this resulted from the increased plasma cortisol levels that are characteristic of pregnancy, that pregnant women do not develop signs or symptoms of hypercortisolism suggests that it is not an excessive level of cortisol but some as yet unrecognized change in steroid metabolism that is responsible for the improvement in arthritic symptoms.

In view of these observations, it seemed more logical in the treatment of arthritics to continue safe, subreplacement dosages of cortisol with temporary increases in times of stress than to withdraw steroid therapy completely. This would apply to patients who apparently achieve a complete remission as well as to those who experience only partial improvement. The practice of continuing some arthritic patients on prolonged therapy with relatively low doses of glucocorticoid is well established in most clinics, but this is done, for the most part, with apprehension and with the intention of ultimately withdrawing the steroid. Because of this philosophy, when a patient achieves a complete symptomatic remission, therapy has customarily been terminated to determine whether the remission would be maintained. Unfortunately, relapses usually occurred.

In addition to rheumatoid arthritis, other autoimmune collagen dis-

orders such as disseminated lupus erythematosus, scleroderma, and polyarteritis nodosa might show favorable responses to persistent administration of small, physiologic dosages of cortisol, but I have not had an opportunity to try this type of treatment in patients with these disorders.

If patients are experiencing a relatively severe exacerbation of any of these collagen disorders, the initial dosage of cortisol probably should be greater to achieve a clinical remission more rapidly, but once the remission is achieved, the continuation of a physiologic dosage indefinitely might prove to have therapeutic advantages without harmful side effects. In other words, treatment of these disorders might be best if it were similar to treatment of adrenal insufficiency; in acute stages, large dosages may be necessary; later, small maintenance dosages may be preferable to discontinuing therapy altogether.

Subsequent reports have confirmed and clarified some of the above impressions that were discussed in the first edition of this book that was published in 1981. These reports resulted from studies by immunologists of an immunoregulatory feedback relationship between the neuroendocrine and the immune system maintained by the hypothalamus-pituitary-adrenal (HPA) axis. In 1985, it was reported that interleukin-1 (Il-1), a protein produced by monocytes in response to inflammatory challenge, stimulated release of ACTH from the pituitary gland.[14] A year later, evidence for the specificity of this feedback and that the production of Il-1 is inhibited by glucocorticoid was reported.[15] This provided an explanation for the inhibition of immunity by large, pharmacologic amounts of cortisol or its derivatives. The following year two other groups [16,17] reported evidence that Il-1 stimulated ACTH release, not by a direct effect on the pituitary, but by stimulating production of corticotropin-releasing factor (CRF) from the hypothalamus. Subsequently, Sternberg and her associates [18,19] reported that a strain of rats that was inherently susceptible to experimental arthritis produced by an injection of a preparation derived from streptococci had defective activation of their HPA axis with a defective CRF production, whereas another strain resistant to such arthritis had a normal CRF response. When the resistant strain had its production of adrenocortical glucocorticoid blocked, it became susceptible to the experimental arthritis. Because the challenge that produced the arthritis in susceptible animals was derived from streptococci, a defect in the immune response of these animals seemed likely.

These observations suggested a possible mechanism for the pro-

duction of rheumatoid arthritis and other autoimmune disorders in humans[20] and an explanation for the beneficial effects of physiologic dosages of cortisol in these disorders in spite of apparently normal customary tests of adrenocortical function. Although patients with rheumatoid arthritis might have blood cortisol and ACTH levels within normal range and might appear to respond to injection of ACTH normally, if their response to stress were defective above the level of the adrenal and pituitary at the level of the hypothalamus, this could explain their aggravation by stress and improvement while taking small, physiologic dosages of cortisol. Under such circumstances, a relative deficiency of cortisol might be present in stressed patients even though their blood cortisol and ACTH levels might be normal for unstressed individuals.

But was there any evidence that this type of defect in the immune response might be present in patients with autoimmune disorders? In 1989, Neeck et al.[21] reported evidence that patients with rheumatoid arthritis had impairment of normal diurnal variation in serum cortisol levels that varied with degree of activity of the arthritis. In 1992, Chikanza et al.[22] reported that patients with rheumatoid arthritis had a lower diurnal rhythm of plasma cortisol levels compared with patients with chronic osteomyelitis and that the rheumatoid patients failed to increase plasma cortisol levels normally following surgery despite having normal responses to administration of CRF, consistent with an interference with the effect of stress on the production of CRF by the hypothalamus.

Hence, patients with rheumatoid arthritis may have potentially normal pituitary and adrenocortical function, but they do not respond normally to at least some types or degrees of stress or to the normal control of diurnal variation due to a defect at the level of the hypothalamus! This defect may not become manifest until a critical threshold of stress is exceeded or a different type of stress is encountered. A similar inadequate adrenocortical responsiveness could result from mild adrenocortical deficiency (low adrenal reserve), but it could be identified more easily by Cortrosyn stimulation tests. Either condition could explain the aggravation by stress, the apparent remissions, and the improvement obtained with small, physiologic dosages of cortisol or cortisone in the patients described earlier in this chapter, and *hence would provide a rationale for prescribing for patients with rheumatoid arthritis prolonged treatment*

with small, physiologic dosages of cortisol plus temporary increases in dosage at times of increased stress.

It also seems likely that other autoimmune disorders may be related to defects in normal HPA responses to stress, a possibility that is discussed further in the chapter on "Other Autoimmune Disorders." This would explain the tendency for patients with any autoimmune disorder to experience exacerbations following sufficient stress and suggests that further studies of the response of the HPA axis to stress in other autoimmune disorders might be helpful. The reasons why one person under sufficient stress develops rheumatoid arthritis whereas another might develop disseminated lupus erythematosus or hyperthyroidism (Graves' disease) or ulcerative colitis or any other autoimmune disorder are undoubtedly pertinent. The well-known familial tendencies for the development of these disorders suggests that hereditary factors play a part in such susceptibilities. It is also possible that patients with any of these disorders might improve if they were given small, physiologic dosages of cortisol with temporary increases at times of increased stress.

Hence, the therapeutic approach to glucocorticoid therapy in autoimmune disorders should be reconsidered. Since treatment of these disorders might involve treatment of deficiencies of cortisol, either relative or absolute, initial dosages of cortisol might need to be higher, but once a remission is obtained, a reduction in dosage to a physiologic replacement level and continuation of this maintenance dosage for the remainder of the patient's life with temporary increases at times of increased stress might be advisable. Experience with the patient in Case 5 in this chapter and with patients with ovarian dysfunction and infertility or with severe allergic disorders in childhood (see p. 107) indicates that such treatment does not interfere with normal development, including puberty and adolescence, having pregnancies and nursing babies.

Stress occurs in two main types: physical and mental or emotional, and frequently these occur simultaneously. For example, the physical stress related to rapid growth and development during puberty is accompanied by varying degrees of psychologic stress that occur during adolescence. During the reproductive years, the stress of bearing and raising children in women and of supporting a family in both men and women occurs, and at the time of the menopause the physiologic stress of hormonal changes in women is accompanied by the psychologic stress of this evidence of aging. In some cases, a history of more severe

physical or emotional stress, such as the tragic death of a loved one, precedes the development of autoimmune disorders by intervals of up to several months. The fact that autoimmune disorders occur more frequently in women and at or following these times of increased physical and emotional stress is consistent with a possible relationship to normal physiologic stresses as well as to other stresses that may occur in both women and in men. Because of the onset and aggravation of rheumatoid arthritis after periods of increased stress, it is probably important not only to increase the dosage of cortisol commensurate with the degree of increased stress, but also, as soon as optimum benefit is obtained, to taper the dosage to maintenance levels as quickly as possible without causing a return of symptoms.

Case 5 also provides an example of another factor that must be remembered in the treatment of any patient with a hormonal deficiency: namely that optimum effects of any hormone may depend upon adequate effects of other hormones (the permissive effect of Ingle[23]). Hence, her beneficial effect of cortisol was obtained while she was taking an adequate dosage of thyroid hormone for her adolescent goiter. It is therefore advisable to consider, and to test and treat, abnormalities in the function of any other endocrine glands that might accompany the endocrine disorder under primary consideration. This principle obviously applies to the treatment of all endocrine disorders.

The place of DHEA in the development and treatment of rheumatoid arthritis remains to be determined. Its failure to be protected by a patent has unfortunately resulted in its receiving relatively little attention, but its apparent relationship to normal menstrual function and to at least some cases of rheumatoid arthritis suggests that it should be studied further, especially in clinical investigations. The low DHEA and androsterone excretion by the five women with rheumatoid arthritis reported in 1967[2] suggests that a combination of low androgen production plus impaired cortisol production in response to stress may contribute to the development of this autoimmune disorder, at least in some cases. If this is true, a combination of physiologic dosages of cortisol plus physiologic dosages of DHEA may be necessary for optimum benefit in such cases. Hence, further studies of the pattern of adrenocortical steroid production and excretion under various degrees of stress in patients with rheumatoid arthritis and other autoimmune and stress disorders should be helpful.

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Chapter 7

ALLERGIC DISORDERS

The effectiveness of large doses of glucocorticoids in the treatment of bronchial asthma and other acute allergic phenomena is well known, but the dosages employed are sufficient to cause hypercortisolism with its undesirable and hazardous side effects if they are continued as maintenance therapy. The use of prolonged glucocorticoid therapy in chronic allergies has, therefore, been discouraged.

With the knowledge that physiologic dosages of cortisone acetate or cortisol may be continued indefinitely without harmful side effects, plus that a number of patients who were given physiologic dosages for other reasons have reported impressive symptomatic improvement in their allergic conditions, it would be advisable to determine whether administration of physiologic dosages for prolonged periods might be helpful in any chronic allergic disorder.

The rationale for this type of therapy is supported by the observation, mentioned in Chapter 4 in the discussion of low adrenal reserve, that many patients with allergies have abnormal ACTH tests, with evidence either of low adrenal reserve or of a low baseline plasma cortisol level. This suggests that allergies may be associated with an abnormality of adrenocortical function in the cases with low adrenal reserve, or of hypothalamic or pituitary function or of glucocorticoid transport in those with low baseline plasma cortisol levels.

A number of animal studies also support the rationale for this type of therapy in allergic rhinitis, allergic asthma, anaphylaxis, and some urticarias, the so-called "immediate-type" hypersensitivity disorders or Type I reactions of Coombs and Gell.[1] This type of allergy is characterized by increased levels of histamine in affected tissues, and administration of histamine can produce Type I allergic reactions. It has been demonstrated that adrenalectomy results in accumulation of histamine in tissues,[2] associated with a reduction of histaminase, the enzyme that destroys histamine,[3] whereas administration of cortisol restores histami-

nase activity and causes depletion of tissue histamine stores. Also, cortisol has been reported to inhibit histidine decarboxylase, the enzyme responsible for conversion of histidine to histamine.[4] Hence, cortisol inhibits the production and accumulation of an excess of histamine in tissues.

Studies[5] in patients with extrinsic asthma have shown that their symptoms are worse when plasma histamine is high and circulating epinephrine is low, and their symptoms are least when plasma histamine is low and circulating epinephrine is high. For a person on a normal sleep-wake schedule, the maximum level of plasma histamine and minimum level of plasma epinephrine are reached at about 3 AM, about four hours after plasma cortisol reaches its lowest diurnal level. Normal subjects showed circadian changes in epinephrine levels similar to those of asthmatics, but the nocturnal rise in plasma histamine in normals was only 1.5 mmol/l compared with 14 mmol/l in asthmatics! The reason for this difference was not clear, but it undoubtedly was related to symptomatology.

Why persons with Type I allergic disorders should have an excess of histamine therefore is not known, but the observation that physiologic dosages of cortisone or cortisol can produce symptomatic improvement suggests some fundamental disorder in this aspect of their immune response, and the evidence that many, if not all, patients with allergic disorders have either low baseline plasma cortisol levels or low adrenal reserve suggests that a relative deficiency of cortisol may be a contributing factor to the excess of histamine.

A report of Venter and associates[6] suggests another factor that may contribute to the development of allergic rhinitis and asthma. They identified autoantibodies to $ß_2$-adrenergic receptors in the serum of one patient with allergic rhinitis and two patients with asthma. Such antibodies may provide a mechanism for ß-adrenergic resistance at the receptor level. Here again the chief product of the body that counteracts autoantibodies is cortisol.

Practically every patient who has had allergies associated with ovarian dysfunction or other disorders for which small dosages of cortisone or cortisol were given has reported improvement in the allergies during this therapy. The beneficial effect of a small dosage of cortisol in a patient with chronic allergic rhinitis and sinusitis was mentioned in Case 2 in Chapter 5. Another impressive example is a girl who experienced decrease in bronchial asthma while being treated with low dosage glucocorticoid therapy for other problems.

Case 1

This patient was referred by her pediatrician at the age of fourteen years because of symptoms of hypothyroidism. During the previous year, she had become chronically fatigued, sensitive to cold, her skin had become dry, and she had developed constipation. The menarche had occurred eighteen months previously, and her cycles had been quite irregular with intervals up to six months, menses lasting ten to fourteen days. Her growth had slowed, and she had gained over ten pounds. Her schoolwork had continued to be excellent, however, with straight *A*'s on her report card. She also had a history of intermittent bronchial asthma since age five, with increased symptoms in the previous two years.

Examination revealed a height of 58 inches, weight 102¼ pounds, blood pressure 90/60, pulse 68 and regular. Her skin was cool. The thyroid gland was diffusely enlarged, approximately twice normal size, with normal texture. There was no lymphadenopathy. Breast development was normal. Reflexes were equal and hypoactive with slow relaxation of ankle jerk. T_3 sponge uptake and T_4 were both low; a thyroid antibody test was negative, but chronic thyroiditis still seemed likely.

She was given Synthroid, 0.1 mg daily, with improvement in fatigue, sensitivity to cold, dry skin, and constipation over the next month, but her asthma became worse. Her baseline plasma cortisol was 15 mcg% at 10:15 AM; and thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 29 mcg%.

Because of the presence of irregular menses and of a thyroid condition suggesting chronic lymphocytic thyroiditis, cortisone acetate, 5 mg four times daily, was added to her therapeutic program. She returned a month later reporting impressive improvement in all symptoms including the asthma. Her weight was 92 pounds, blood pressure 100/70, pulse 76 and regular. Basal temperature chart showed a normal 32 day ovulatory cycle.

Subsequently, she maintained an optimum thyroid state with Euthroid, gr 1 twice daily, plus cortisone acetate, 5 mg four times daily. The thyroid decreased almost to normal size, and her asthma remained in remission except during several respiratory infections, which responded to treatment more quickly than prior to cortisone therapy. During respiratory infections, cortisone acetate was increased to as much as 20 mg four times daily, depending upon severity of the illness, and symptoms cleared in less than a week with no recurrences, in contrast to previous respiratory infections that had been much more severe and lasted for several weeks. Whenever evidence of bacterial infection was present, she was given either penicillin or erythromycin in therapeutic dosages in addition to an increased dosage of cortisone acetate and experienced rapid improvement. The patient, her mother, and her pediatrician were all impressed by her improvement while receiving the small dosage of cortisone.

In addition to numerous typical symptoms of hypothyroidism, this fourteen-year-old girl had irregular, prolonged menses and bronchial asthma. The presence of a goiter suggested a chronic thyroiditis even though anti-microsomal and anti-thyroglobulin antibodies were not de-

tected. This did not rule out the possibility of chronic autoimmune thyroiditis because it is now known that antibodies other than the ones tested for in this patient may occur.[7] An ACTH test was borderline low, so there was no clear indication for cortisone therapy, yet it produced dramatic improvement in her asthma and in her ability to recover from respiratory infections as well as in her menstrual cycles.

Case 2 is that of an older asthmatic who experienced impressive improvement while taking a small dosage of cortisol.

Case 2

This woman was first seen at the age of sixty-three with asthma of ten years duration and chronic respiratory infections with sinusitis and fatigue for the previous two months. She had had a hysterectomy for fibroids at age thirty-five, having bled intermittently for two years. Her cycles had previously been normal and she had had three full-term pregnancies.

Temperature tolerance had been normal, bowels had been regular, and she never had any hot flashes. She had been given injections for her asthma, but she had received no estrogen therapy. Increased hair growth on her chin had been noted for the previous five years. Six years previously a nodule in the thyroid had been removed, but no thyroid medication had been given. Her mother and sister had had goiters removed.

Physical examination revealed moderate hirsutism of the face, periareolar and subumbilical areas, and extremities. She had a residual suntan in February from the previous summer. Weight was 138¼ pounds, blood pressure 138/74, pulse 84 and regular. The thyroid scar was well healed, and there was no thyroid tissue palpable in the neck. Bilateral wheezes but no rales were present over both lungs. The liver edge was palpable, one finger-breadth below the right costal margin, not tender. T_3 sponge uptake was 41%, and T_4 was 10.2 mcg%. Urinary 17-KS were 7.0 mg/24 hours, and 17-OHST 8.2 mg/24 hours. Plasma cortisol at 8 AM was 10.0 mcg%; and an hour after an I.M. injection of 25 units of ACTH, this rose to 45.0 mcg%. She volunteered that her asthma improved for four days after the ACTH test. She was therefore given a trial of cortisol, 5 mg four times daily.

She returned a month later reporting impressive improvement in her asthmatic symptoms, with less wheezing, better energy, and better appetite. After this improvement had been maintained for six months, the dosage was decreased to 2.5 mg four times daily. Shortly after the decrease, she developed a mild respiratory infection, and her symptoms of asthma became worse, so a dosage of 5 mg four times daily was resumed, and she continued to take this dosage. Meanwhile, her liver edge became no longer palpable. In the spring of 1976, she had no respiratory infections or influenza, although most of the other workers at her place of employment were sick in an influenza epidemic.

Three months later, the cortisol dosage was decreased to 5 mg before each meal and 2.5 mg at bedtime, and a week later she developed symptoms of pneumonia with a recurrence of bronchitis. This responded to antibiotics plus Marax®. Six months later, she had a recurrence of asthmatic bronchitis that responded to prednisone, 5 mg four times daily, and aminophyllin that were prescribed by another physician. Cortisol was resumed at 5 mg four times daily, prednisone dosage being tapered and discontinued, and she was quite well for the subsequent two years that she was followed. It was apparent that this patient was healthier on a dosage of 5 mg cortisol four times daily than on any smaller dosage, yet this dosage was barely sufficient to control her allergic symptoms.

These cases also indicate that patients with allergic disorders may improve with small, physiologic dosages of cortisol or cortisone even though their Cortrosyn stimulation test results fall within normal range, suggesting a deficient stimulation of their adrenals by their pituitary glands. In addition, they are examples of the increased incidence of allergies and autoimmune disorders at times of increased physiologic as well as psychologic stress, namely puberty and the menopause.

Case 3 provides additional evidence for the safety and effectiveness of physiologic dosages of cortisol in patients with chronic allergies plus demonstrating that physiologic dosages of cortisol not only do not impair normal growth and development, but may actually help to restore it. Bronchial asthma is one of the more severe manifestations of allergy, but other types of allergy can also seriously interfere with growth and health, as is evident in this case.

Case 3

This patient was referred at age 10 by an allergist because she was about 20 pounds underweight, a condition that had apparently developed over the previous three years. At age 2, she had demonstrated evidence of being allergic to eggs (vomited), and since age 9 she had experienced a similar reaction to milk. Her energy seemed normal, but she required 12 hours sleep and was sensitive to cold. She had had frequent upper respiratory infections and two months previously an attack of respiratory flu. Her mother had hay fever, but there was no other family history of allergy or endocrine disorders. Physical exam was not remarkable except for her being underweight, with a few small, non-tender nodes palpable in the right posterior cervical chain. Height was 56 inches, weight 59½ pounds, blood pressure 90/60, pulse 64, WBC 10,000, with 21% eosinophiles. T_3 by RIA was 170 ng/dl, baseline cortisol was 6.1, and 30 minutes post-Cortrosyn cortisol was 26 mcg/dl. Because of her low baseline cortisol, a therapeutic trial with cortisol, 5 mg four times daily, was

given with impressive improvement in her allergies and she began to gain weight. Nine months later her thyroid was slightly enlarged with a T_3 by RIA of 185 ng/dl, and Euthroid, gr ½ daily, was added.

Five months later her height was 57½ inches, weight 66½ pounds, blood pressure 80/50, pulse 88, and she had missed no days from school for the first time in her life. Immune globulins were interesting: IgG was slightly low, IgA normal, IgM low normal, and IgE markedly elevated (1590 U/ml, with normal less than 150 U/ml). She continued to grow normally and to gain weight towards normal, and her thyroid was no longer enlarged. After she had been taking cortisol for 15 months, it was decided to taper and stop the cortisol and repeat lab tests two weeks later, but the second day after stopping cortisol she developed a sore throat, headache, and fever of 102 degrees. WBC was 9,600 with 66% neutrophiles and 6% eosinophiles, so Cortef was resumed with a course of penicillin. Euthroid was continued. After an uneventful recovery, WBC was 8,600 with 37% neutrophiles and 21% eosinophiles, so the dosage of cortisol was increased to 7.5 mg four times daily. She felt better on this larger dosage, and she continued to gain weight normally with few if any allergic symptoms.

At age 12, the cortisol dosage was decreased to 5 mg four times daily, but she lost 8 pounds, became tired and sleepy and developed an upper respiratory infection. WBC was 9,100 with 60% polys, and 2% eosinophils. T_4 was 8.2, T_3 by RIA was 145. Cortef was increased to 10 mg four times daily with prompt recovery from the URI, then decreased to 7.5 mg four times daily, a dosage that both the patient and her mother thought best for her overall health and energy. At age 13, thyroid medication was stopped without apparent change. At age 14, while she was attending high school, her schedule of cortisol was changed to 10 mg every eight hours. Shortly after that she had a normal menarche with regular, normal cycles. She continued to feel well, with good energy and excellent scholastic work (she was an honor student).

At age 17, she reached her ultimate height of 65¾ inches and weight of 114 pounds. During the school year she changed her dosage schedule to 10 mg twice daily, before breakfast and supper, with a slight return of seasonal hay fever and occasional URI. During summer vacation she took cortisol, 5 mg four times daily, but her plasma ACTH level was found to be elevated (156 pg/ml, with an upper normal level of 82), so her cortisol dosage was increased back to 7.5 mg four times daily with a gradual return of ACTH back to normal (31 pg/ml) over the next 4 years. Throughout her school years she continued being an honor student.

At age 22, her thyroid gland was again slightly enlarged, so Synthroid, 0.05 and later 0.1 mg daily, was resumed. At age 28, she was leading an active life and holding a responsible job. Another attempt was made to taper her dosage of cortisol, but by the time her dosage was decreased to ½ tablet (2.5 mg) three times daily she was "miserable. Foods that I have eaten for years suddenly bother me. My weight is dropping. I have experienced everything from hives, canker sores, and acne, to sneezing, itchy eyes and throat, headaches and overly dry skin." She was therefore advised to resume her previous dosage of cortisol (7.5 mg four times daily), and it seems likely that she will need to continue it with temporary increases during res-

piratory infections or other stresses for the rest of her life. She has been assured that this medication will not interfere with her having a normal life, including getting married and having children if she so desires, since over 200 babies have been born to women taking cortisol or cortisone acetate in these small, physiologic dosages throughout their pregnancies and nursing periods without evidence of harm to either mothers or babies (see p. 84).

This case presents several interesting points. It clearly indicates how severe allergies can interfere with normal growth and development, and how physiologic dosages of cortisol can not only relieve the symptoms of allergy, but also help to restore normal growth and development, in contrast to the well known harmful effects of large, pharmacologic dosages of glucocorticoids. During puberty and adolescence, when her body was undergoing increased physiologic stress, her dosage requirements for cortisol temporarily increased slightly, then returned to previous levels when this stress subsided, but the maintenance dosage never reached that of a replacement dosage for a totally adrenalectomized patient. Another time of increased physiologic as well as psychologic stress is the menopause, so a slight increase in dosage of cortisol for mildly adrenally insufficient patients at that time of life may be helpful. Because the adrenals are such dynamic glands, temporary increases at times of other stresses such as respiratory infections are helpful, but the dosage should return to the usual maintenance level as soon as the patient recovers to avoid development of hypercortisolism. During pregnancies, an optimum amount of cortisol seems to be necessary to maintain the delicate tolerance of the mother for her baby that is essentially a foreign body to her immune system, so an inadequate amount can lead to a miscarriage, as is discussed in Chapter 5.

The association of allergic disorders with excessive production of IgE are well known, but the effects of physiologic amounts of cortisol upon all immune globulins should be studied further, especially since a physiologic amount of cortisol has been shown to increase the production of immune globulins by B cell lymphocytes.[8] In this case, immune globulins were not measured until she had been taking cortisol for over a year, but they were still quite abnormal, even though she was clinically much improved. They were not studied further because of limited research funds.

There was also evidence that this patient needed thyroid medication to avoid developing a goiter, but her thyroid deficiency was not sufficiently great to interfere with normal cortisol effect or with normal ado-

lescence while she was receiving adequate cortisol. The decrease in her excessive level of blood eosinophils during respiratory infections was interesting, suggesting that her immune response to respiratory infections took precedence over her allergic tendency since she had not increased her dosage of cortisol at the time blood was drawn for differential counts.

Her history suggesting lactose intolerance in childhood caused some concern because cortisol tablets contain lactose in the filler, but she tolerated the tablets without difficulty. Her Cortrosyn tests also raised an interesting question, in that her initial test at age 10 was consistent with low cortisol secondary to decreased production of ACTH, but at age 17 after decreasing her dosage of cortisol to 5 mg four times daily, her ACTH level was elevated, consistent with primary adrenocortical deficiency. Could her improved nutritional as well as improved hormonal status have restored her pituitary production of ACTH and revealed a primary adrenocortical deficiency?

These observations suggest that further studies of the HPA axis and of the effects of physiologic dosages of cortisol on patients with chronic allergies should be helpful not only in determining optimum therapeutic management, but also in learning more about the etiology of allergic disorders.

Patients with seasonal allergies may benefit from taking small, physiologic dosages of cortisol in the spring or autumn, with temporary increases depending upon the severity of symptoms. It is also advisable to obtain Cortrosyn stimulation tests on these patients, because they may find that their health and energy are better if they take a physiologic dosage of cortisol throughout the year.

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Chapter 8

OTHER AUTOIMMUNE DISORDERS

For many years, it has been known that allergies are disorders of the immune response, but only relatively recently has it been recognized that rheumatoid arthritis and other collagen diseases are associated with a disturbance of the immune system, wherein the body develops antibodies or immune complexes that damage some of its own tissues. With recent advances in the techniques for recognizing disorders of the immune mechanism, a number of other clinical conditions have been found to be associated with autoimmune phenomena. These include hyperthyroidism with diffuse goiter (Graves' disease), chronic lymphocytic thyroiditis (struma lymphomatosa), diabetes mellitus, regional enteritis, and ulcerative colitis. The possibility of beneficial effects of physiologic dosages of glucocorticoids has been suggested in each of these prior to the demonstration of their autoimmune basis, so now it is even more desirable to determine the potential contribution of this therapy in their management.

HYPERTHYROIDISM WITH DIFFUSE GOITER

In 1930, Marine[1] postulated that Graves' disease was associated with adrenocortical insufficiency. Both conditions are characterized by enlargement of the lymph nodes associated with a relative lymphocytosis. When cortisone first became available, it is not surprising that therapeutic trials of its administration to patients with this disorder were made. Hill, Reiss, Forsham, and Thorn, in 1950,[2] reported that cortisone acetate, in doses of 100 to 200 mg per day for sixteen days, produced a decrease in serum protein-bound iodine and basal metabolic rate in a patient with Graves' disease. This group also reported that "following an initial exacerbation of clinical hyperthyroidism (manifested chiefly by an increase in basal metabolic rate) both ACTH and cortisone appear to suppress thyroid function in about one half of the patients with Graves'

disease in this limited series." The clinical improvement in one patient given ACTH was so impressive that a subtotal thyroidectomy was performed with no other antithyroid medication!

In 1951, Rawson[3] stated that the adrenals of some hyperthyroid patients were not normally responsive to ACTH, and Lerman[4] stated that with tests of adrenal function available at that time, patients with Graves' disease appeared to have lowered adrenocortical function with inadequate response to stress.

Wikholm and Einhorn,[5] in 1963, reported that 60 mg prednisolone daily for seven days to patients with hyperthyroidism produced a significant decrease in I^{131} uptake and an impressive decrease in serum protein-bound iodine. In 1964, Snyder, Green, and Solomon[6] reported that prednisone in doses of 40 to 60 mg daily resulted in disappearance of long-acting thyroid stimulator (LATS) from the serum of two patients with ophthalmopathic Graves' disease.

Such dosages were too large to be tolerated for extended periods, but the observations suggested that glucocorticoids might have a beneficial effect upon Graves' disease. With later evidence that LATS is an abnormal immune globulin, Graves' disease became classified as an autoimmune disorder. Although it was not known why glucocorticoids were beneficial in autoimmune disorders, nor why larger dosages were required to produce beneficial effects in some cases than in others, the supplementation of antithyroid therapy with safe, physiologic dosages of cortisone acetate or cortisol seemed to warrant further study.

These speculations, which were made in the first edition of this book, have been confirmed and extended by studies that were discussed in Chapter 6. It is now known that autoimmune disorders may be produced by abnormal responses of the HPA axis to stress, but it is not yet known why one person might respond to increased stress by developing autoantibodies to certain of his or her tissues, whereas another might develop autoantibodies to other tissues or might develop high blood pressure or peptic ulcers or mental disorders or any of the other conditions that are known to be related to stress. Undoubtedly familial inherited factors contribute, but the manner in which they contribute must be determined, as well as the manner in which the HPA axis is involved.

Favorable effects of pharmacologic dosages of cortisone in patients with thyroid storm[7] or with severe ophthalmopathy associated with Graves' disease[7,8] were also reported. These disorders are rare complications of

Graves' disease, but glucocorticoid therapy has remained a valuable adjunct in their therapy. As with other severe disorders, initial dosages have been relatively high. The observations of Brown and his associates[8] indicated that large dosages were necessary to produce a remission in severe ophthalmopathy. Continuation of such dosages may produce serious side effects, however, yet when they are tapered and withdrawn altogether, relapses often occur. As soon as the ophthalmopathy has been brought under control, therefore, dosages for our patients have been reduced to physiologic levels and have been continued for months or even years. Such patients seemed to maintain remissions better and have fewer relapses than those who discontinued the steroid altogether. The advisability of administering small dosages of cortisone acetate or cortisol to patients with Graves' disease without severe ophthalmopathy was therefore considered, and routine ambulatory ACTH tests on patients with this disorder were initiated.

As a consulting endocrinologist, I have not seen many cases of uncomplicated Graves' disease, since most of these have been treated by primary care physicians. Hence, the cases referred to me tended to be more complicated therapeutic problems, but their response to this therapeutic approach was encouraging. Patients who have been treated in this manner have reported improvement in energy and a decrease in nervousness to a degree that warrants further investigation. Important questions regarding its possible advantages are whether it improves the percentage of patients receiving permanent remissions from customary medical therapy and whether continuation of small, safe, physiologic dosages of cortisol indefinitely may be advisable.

A patient who exemplifies the value and safety of this type of therapy in moderately severe ophthalmopathy and pretibial myxedema was referred to me at the age of thirty-nine years because of exophthalmos.

Case 1

The patient had been married at age twenty-eight and had a full-term, normal delivery ten months later. Subsequently, she had seven successive miscarriages, three in the first trimester and four at approximately six months gestation. During her fourth pregnancy, at age thirty-five, she developed hyperthyroidism and was treated with propylthiouracil and a subtotal thyroidectomy. Subsequently, she developed hypothyroidism, and thyroid medication in doses up to gr 6 daily had been given with some improvement. During this time she developed exophthalmos and marked swelling and thickening of the skin of the left leg and slight swelling and

thickening of the skin of the right leg. At age thirty-seven, her thyroid medication had been changed to Cytomel®, 100 mcg daily. She continued to be sensitive to both heat and cold; her hands and feet would get cold easily, but she perspired rather heavily.

Physical examination revealed no tremor; blood pressure was 112/85, pulse 92 and regular, weight 134 pounds, height 66½ inches without shoes. There was bilateral puffiness of the periorbital tissues, with marked lid retraction and slight chemosis of the bulbar conjunctivae. Extraocular movements were within normal limits except for slight diplopia on looking far to the right. Exophthalmometer readings were 26 mm on the right and 25 mm on the left (normal = 18–20 mm). The thyroid was not palpable. Severe pretibial myxedema was present on the left leg with much brownish discoloration and induration, and mild pretibial myxedema on the right leg. A thyroidectomy scar was present but not pigmented. Serum PBI was 1.6 mcg/100 ml, and cholesterol was 127 mg per 100 cc. Urinary 17-KS were 10.0 mg and cortisol metabolites 9.9 mg/24 hours.

The PBI and cholesterol were consistent with an excessive dosage of triiodothyronine, since this medication does not contribute to serum PBI, and her exophthalmos and thyroid status improved after a decrease to 12.5 mcg of Cytomel twice daily plus 0.15 mg daily of Synthroid. Exophthalmometer measurements decreased to 24 mm bilaterally, but pretibial myxedema did not improve until prednisolone, 2.5 mg four times daily (comparable to cortisol, 10 mg four times daily), was added. On this regimen, the pretibial myxedema improved progressively. A year later she conceived again. PBI was only 3.6 mcg%, so the dosage of thyroxine was increased to 0.3 mg per day. PBI then increased to 10.5 mcg%. At six months gestation, the dosage of prednisolone was decreased to 1 mg four times daily. On this program, she had a full-term delivery of a normal infant by caesarean section. After delivery, thyroxine dosage returned to 0.15 mg daily, and nine months later the prednisolone was changed to cortisone acetate, 5 mg four times daily.

The patient was subsequently followed at intervals up to age 56, seventeen years after she was first seen. Her thyroid status remained stable, her exophthalmos improved, with exophthalmometer readings remaining between 24 and 25 mm bilaterally, and her pretibial myxedema cleared completely. Her maintenance medications consisted of Euthroid, gr ½ twice daily, and cortisol, 5 mg four times daily. An ACTH test at age 56 revealed a baseline plasma cortisol at 10:30 AM of 19 μg/dl; 30 minutes after an I.M. injection of 25 units of Cortrosyn this rose to 30 μg/dl.

Although ophthalmopathy and pretibial myxedema apparently developed while the patient had postoperative hypothyroidism, it was evident that excessive replacement with triiodothyronine did not help and may have aggravated this complication. Subsequent improvement in ophthalmopathy and clearing of pretibial myxedema with smaller dosages of thyroid medications plus physiologic dosages of glucocorticoid was impressive, and her successful, full-term, normal pregnancy after having

had seven successive miscarriages indicated that her general hormonal status had improved.

Case 2 also demonstrates the beneficial long-term effects of low doses of cortisol in ophthalmopathy associated with Graves' disease, but the patient is, in addition, an example of several other problems worthy of comment.

Case 2

This fifty-six-year-old female was referred because of an eye problem. Two years previously, she had developed redness and irritation of both eyes. She had been taking Aldomet® for high blood pressure for four years, but her health had otherwise been good. A physician had told her the inflammation was probably due to an infection, and she was given drops which she used for two months without benefit. Four months later, she was admitted to a hospital for studies, and tests suggested mild hyperthyroidism. She was given propylthiouracil, 200 mg four times daily, plus Diuril® and Valium®. Aldomet was continued.

After taking the propylthiouracil for six months, she was admitted to another hospital by a different physician, who had her stop all previous medications for three months. During this time her eyes became much worse, with more prominence and inflammation. She had then been given large doses of prednisone, which were subsequently tapered and discontinued three months later. A scan was performed, and she was told that her thyroid was normal. Three months later an ophthalmologist performed a decompression operation on both orbits, followed in four months by a muscle resection for diplopia. Prednisone, 25 mg every other day for a week, then nothing for a week, was administered for six weeks. She was then referred to me. At the time of referral she was taking only Aldomet, one tablet daily.

She had been sensitive to heat all her life. At age twelve, she was told she had "a tendency to a goiter." She also noted occasional diarrhea. Eighteen months before referral, she sometimes felt "trembly," and her appetite was "too good." She gained 30 pounds with prednisone treatment, her usual weight being 140 pounds. Arthritic pains in her hands and sacroiliac area were relieved with the prednisone, but this therapy caused extreme weakness.

Past history included severe pneumonia at nine months of age, many "bronchial troubles," and a tendency to catch colds that settled in her chest. A cholecystectomy for stones was performed at age forty-one. The menarche occurred at age twelve, cycles had been regular, but she had much dysmenorrhea. She had only one pregnancy with a normal, full-term delivery. No further pregnancies occurred in spite of a lack of precautions. The menopause occurred at age forty-seven, with hot flashes for which she had received "hormone shots" every six weeks for several months. Family history was negative for thyroid disorders, but both parents had high blood pressure.

Physical examination revealed a height of 63½ inches, weight 171 pounds, blood pressure 160/100, pulse 108 and regular. There was moderate periorbital puffiness

and moderate injection of the sclera. Slight widening of the palpebral fissure was present on the left with diplopia in all directions except slightly below the horizontal. Extraocular movements of the right eye were within normal limits, but there was slight impairment of upward and lateral gaze with the left eye. Exophthalmometer readings were 30 mm on the right and 29 mm on the left eye. The thyroid was not definitely palpable. There was no tremor. T_3 sponge uptake was 59%, T_4 6.1 mcg%. Plasma cortisol at 8:45 AM was 33.0 µg/dl; thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 45.5 µg/dl.

The patient was given saturated solution of potassium iodide, 5 drops daily, Cortef, 5 mg four times daily, Multicebrin®, 1 daily, and Euthroid, gr ½ daily, and gradual improvement occurred. Blood pressures were in upper normal range, and Aldomet was discontinued without change. After two years of this therapy she continued to feel well, and she had no further arthritic pains. Slight puffiness of the periorbital tissues persisted with extraocular movements within normal limits. Diplopia was no longer present except on extreme upward gaze. Exophthalmometer readings were 24 mm bilaterally, blood pressure 160/90.

It is not unusual for the diagnosis of endocrine ophthalmopathy to be missed. Whenever a patient with a history of Graves' disease develops eye problems, it should be suspected, but when a patient with no history of thyroid disorder presents with inflammation of the eyes, it is certainly not the first diagnosis to be considered. Nevertheless, unless it is considered, much time may be lost. Even when it is suspected, other conditions such as conjunctivitis or tumor of the orbit should be ruled out. When the diagnosis is made, the use of propylthiouracil, especially in large dosages, may not be the best antithyroid therapy. Mild hyperthyroidism with ophthalmopathy seems to respond better to iodide, with the addition of thyroxine if the patient becomes hypothyroid.[7]

Propylthiouracil in the relatively large dosage of 200 mg four times daily should be reserved for patients with severe hyperthyroidism, and I prefer to avoid the thiourea derivatives in patients with severe ophthalmopathy. Furthermore, although diuretics have been reported to be symptomatically helpful in severe exophthalmos, glucocorticoids are much more effective. The use of tranquilizers in hyperthyroidism also seems logical, but except for reserpine or propranolol in certain cases, other tranquilizers have not been very helpful.

The patient then sought advice from another physician, and he had her stop all previous medications for three months. This probably was unwise, because not only is it more difficult to evaluate thyroid status after antithyroid drugs are withdrawn, but also relapses may occur more

abruptly. It is better to study patients while they are on their previous therapeutic program, unless they are having a toxic reaction to a medication. Therapy can then be changed as indicated, but only relatively slowly. Rapid changes in endocrine therapy sometimes seem to cause additional problems, as occurred in this case.

The exacerbation of ophthalmopathy following withdrawal of medications was treated with large doses of prednisone with temporary improvement, but discontinuance of this therapy after three months was followed by another relapse that resulted in bilateral decompression operations. Such surgical procedures are advisable as last resort measures to prevent loss of sight, but if suitable medical therapy, including treatment with saturated solution of potassium iodide, glucocorticoids, and small doses of thyroxine or thyroxine plus triiodothyronine if hypothyroidism develops, is administered on a consistent, stable program, surgery rarely seems to be necessary.

The development of weakness on prednisone therapy suggests the development of hypokalemia, a relatively common complication of large dosages of glucocorticoids administered for prolonged periods. In my experience, dosages of 20 mg prednisone daily may be needed in acute endocrine ophthalmopathy, but they should be tapered as rapidly as possible as soon as the acute inflammatory state begins to subside, and, as mentioned previously, I prefer to prescribe the normal hormone, cortisol, instead of stronger derivatives.

Two recent reviews summarize the present state of knowledge regarding the etiology and immunology of the autoimmune aspects of thyroid disease.[9,10]

Case 3

A twenty-three-year-old female patient was referred by her obstetrician in the third month of her first pregnancy because of hyperthyroidism. For three months she had suffered increased nervousness, tremor, and a tendency to diarrhea. She had lost some weight, but this had been attributed to morning sickness. T_3 sponge uptake had been 39%, and T_4 had been greater than 13.0 mcg%. The menarche had occurred at age thirteen or fourteen; cycles had always been irregular with intervals of twenty-eight to sixty days, menses lasting seven days with a heavy flow and cramps. She had experienced severe headaches two days premenstrually.

Physical examination revealed slight widening of the palpebral fissures, moderate tremor, and a diffuse enlargement of the thyroid gland approximately one-and-one-half times normal size. Height was 60¾ inches, weight was 107¾ pounds, blood

pressure 114/70, pulse 100 and regular. T_3 by RIA was 335 ng/ml (normal 90–200). A thyroid antibody test was negative.

A diagnosis of mild hyperthyroidism in the third month of pregnancy was made, and she was given a prescription for saturated solution of potassium iodide, 5 drops daily in milk. She returned a week later reporting some improvement in nervousness, but she was still chronically fatigued with much aching of her muscles, and she continued to have frequent nausea and vomiting. Weight was 109¼ with sandals, blood pressure 118/70, pulse 104 and regular. Moderate tremor, slight stare, and enlargement of the thyroid gland were unchanged. Plasma cortisol at 2 PM was 25 µg/dl. Because of her history of irregular menses, cortisone acetate, 5 mg four times daily, was added to her therapeutic regimen. An antacid was administered with each dose of cortisone because of the nausea associated with pregnancy.

She returned two weeks later reporting some improvement, but she was still depressed and nervous, with much nausea and insomnia. Tremor was no longer present, weight was 114 pounds, blood pressure 110/60, pulse 80 and regular. T_4 was 8.3 mcg%.

A month later she returned feeling much better; nausea had subsided, nerves were calm, and she was sleeping well.

The remainder of her pregnancy was normal and uneventful. The potassium iodide was discontinued six weeks before delivery, but cortisone acetate was continued up to delivery, which was performed by caesarean section because of a narrow pelvic outlet. No supplementary glucocorticoid was given at the time of her caesarean section, which she tolerated well.

She chose not to nurse her baby. Cortisone acetate and potassium iodide were resumed when she was able to take oral medication postpartum. Six weeks postpartum, her obstetrician had her start an oral contraceptive. She had no complaints six months later. Her thyroid had increased slightly to approximately two-and-one-half times normal size, but she had no other signs or symptoms of thyroid disorder, weight being 113½ pounds with shoes, blood pressure 110/70, pulse 76. Potassium iodide was continued temporarily, and, if her condition remained stable, cortisone acetate was planned to be discontinued.

Because of her history of menstrual irregularity, an ACTH test was planned after cortisone acetate had been discontinued, and if her cycles became irregular again, this medication would be resumed. Meanwhile I retired from full time practice and the patient failed to return for further follow-up.

Although this patient might have improved as well on potassium iodide therapy alone, her initial response to iodide treatment was poor, the administration of cortisone acetate was followed by progressive improvement with a full-term delivery of a normal baby, and her thyroid status remained stable for at least six months postpartum.

Although antithyroid drugs such as propylthiouracil or methimazole (Tapazole®) may apparently be used safely to treat hyperthyroidism

during pregnancy, provided proper care is taken to avoid excessive suppression of the thyroid, saturated solution of potassium iodide is still a good therapy for this type of problem, and it avoids the danger of side effects of the thiourea drugs. Because patients with ovarian dysfunction often have their disorder become worse after oral contraceptives, I prefer to avoid their use in such cases, but occasionally the risk of another pregnancy may be sufficiently great and the likelihood of adequate protection by other contraceptive measures sufficiently uncertain so as to justify them as the lesser of two evils.

The safety and effectiveness of physiologic dosages of cortisone or cortisol during pregnancies has been discussed in Chapter 5.

CHRONIC THYROIDITIS

A related disorder in which physiologic dosages of glucocorticoids have therapeutic promise is chronic thyroiditis. This not only applies to chronic lymphocytic thyroiditis, or struma lymphomatosa, which appears to be etiologically related to Graves' disease, but also to at least some other types of chronic thyroiditis. Yamada and his associates[11] have reported beneficial effects of 1 mg dexamethasone orally twice daily in patients with struma lymphomatosa, a dosage of glucocorticoid equivalent to approximately 40 mg cortisol daily and hence approximately twice as large as that used in our practice.

An example of the beneficial effects of low dosage glucocorticoid therapy in nonspecific thyroiditis is Case 4.

Case 4

A thirty-two-year-old female was referred because of a thyroid problem. Nine months previously, she had an attack of "flu" during which her thyroid became swollen and tender and her face became puffy. T_4 was 3.5 mcg% and I^{131} uptake was 53%, with diffuse enlargement of her thyroid gland. She had been given Synthroid, 0.025 mg daily for five months. On this treatment her T_4 was 2.0 mcg%. The Synthroid had then been discontinued, following which she developed progressive sluggishness and sensitivity to cold. She had suffered from bronchial asthma as long as she could remember, for which she had received Quadrinal™ and injections of Aristocort® Forte. Her energy had also been poor as long as she could remember. The menarche had occurred at age twelve, with regular cycles, menses lasting from five to six days. She was married and had two children.

Physical examination revealed a height of 61¾ inches, weight 107 pounds, blood pressure 90/60, pulse 88 and regular. Her hands and feet were cold, and her voice was slightly hoarse. The thyroid was diffusely enlarged two-and-one-half times normal size, not tender. There was no lymphadenopathy. Moderate chronic cystic mastitis was present bilaterally. There was no acne or hirsutism. A thyroid antibody test was negative. T_3 sponge uptake was 40%; T_4 was less than 1.0 mcg%. Sedimentation rate was 8 mm/hour, hematocrit 39%. Plasma cortisol at 2 PM was 12.2 µg%; thirty minutes after an I.M. injection of 25 units of ACTH, this rose to 32.8 µg%.

A diagnosis of hypothyroidism with goiter, probably due to a previous thyroiditis, was made. On Synthroid, 0.15 mg daily, and cortisone acetate, 5 mg four times daily, she had a gradual but dramatic improvement in all of her symptoms, including the bronchial asthma, and her thyroid returned to normal size. Thickening of glandular tissue in the breasts also cleared.

This patient's thyroiditis developed after a viral infection that was diagnosed as "flu," and her treatment with physiologic dosages of thyroid and cortisone not only improved her thyroiditis, but also her bronchial asthma, her chronic cystic mastitis, and her chronic fatigue.

Case 1 in Chapter 6 is an example of the beneficial effect of a subreplacement dosage of cortisol on a more common type of chronic thyroiditis. Case 5 suggests a promising therapeutic approach to the treatment of chronic autoimmune thyroiditis in a young woman.

Case 5

A 16-year-old girl complained of tiring too easily and difficulty concentrating for the previous two or three years. Her hands were always cold and her hair tended to be dry, yet she continued to play varsity basketball at high school. The menarche had occurred at age 14 and menses had been slightly irregular, lasting 7–8 days with heavy flow and occasional severe cramps. She had been taking Armour's thyroid, gr 1 daily, for 2 months, then gr 2 daily for about 8 months with slight improvement. No thyroid tests had been performed. A sister, age 13, was quite energetic. A family history of goiter and diabetes was present.

Physical exam revealed a height of 67½ inches, weight 152 pounds, blood pressure 100/70, pulse 60. Her thyroid was soft, not enlarged or tender. Reflexes were slightly sluggish. Cholesterol was 159 mg/dl, T_3 40.5%, T_4 6.4 mcg%, T_3 by RIA 152 ng/ml, TSH 0.6 mIU/ml, ACTH 34 pg/ml, cortisol 9.7 mcg/dl, 30 minute post-Cortrosyn cortisol 24.4 mcg/dl, and erythrocyte sedimentation rate 6 mm/hour. Thyroid anti-microsomal antibodies were positive in a titer of 1:6400; anti-thyroglobulin antibodies were negative. She commented that she felt better for three days after the injection of Cortrosyn.

Diagnoses of chronic thyroiditis and mild adrenocortical deficiency secondary to inadequate stimulation by her pituitary gland were made. Thyroid medication was changed to Synthroid, 0.15 mg daily, and Cortef, 7.5 mg four times daily, was started, with impressive symptomatic improvement. A year later both thyroid antimicrosomal and anti-thyroglobulin antibodies were elevated, so an increased dosage of Cortef of 20 mg four times daily for 4 days, then 15 mg four times daily for 4 days, then 10 mg four times daily for 4 days, then 10-10-5-5 mg daily thereafter was prescribed. Synthroid, 0.15 mg daily, was continued. Ten months later both thyroid anti-microsomal and anti-thyroglobulin titers were negative.

Meanwhile, she had started attending college and continued to play varsity basketball, taking 30 mg (10-10-5-5) cortisol and 0.15 mg Synthroid daily. A year later both thyroid antibody titers had increased again, so another temporary increase in dosage of cortisol was prescribed as previously. Six months later, thyroid antibodies were again negative and sedimentation rate was normal, so the same maintenance dosage was continued. They were still negative six months later, so she was instructed to decrease her dosage of cortisol to 5 mg four times daily, continuing Synthroid, 0.15 mg daily. Subsequently she finished college and now is holding a responsible job.

Because these are safe, physiologic dosages of normal hormones, when optimum dosages are determined, she will probably need to continue them for the rest of her life, but because of their known safety, they will not interfere with her living a normal life. Hopefully, they will also enable her to keep her chronic thyroiditis in remission. The evidence that her elevated thyroid antibody titers could be returned to normal by a temporary increase in dosage of cortisol suggested that this therapeutic approach might possibly result in a longer lasting or even a permanent remission in her chronic thyroiditis, so this possibility is being pursued.

DIABETES MELLITUS

Another condition in which physiologic dosages of cortisol appear to have therapeutic benefit is diabetes mellitus. This undoubtedly would come as a surprise to many, because a characteristic effect of excessive dosages of glucocorticoid in diabetics is an increase in blood sugar levels and an increased requirement for insulin. Yet, a number of patients with diabetes mellitus experience marked fluctuations in blood sugar levels with swings from hyperglycemia to hypoglycemia, resulting in difficulty of control and much clinical distress. The ultimate manifestation of this disorder of labile diabetes mellitus is seen in patients with both diabetes mellitus and adrenal insufficiency where the body's

mechanisms for protection against both high and low levels of blood sugar are impaired. Although epinephrine, glucagon, and growth hormone also help to protect against hypoglycemia, the presence of adequate levels of glucocorticoid seems to be of primary importance, since in adrenal insufficiency the endogenous supply of the other hormones does not prevent insulin hypersensitivity and hypoglycemia. This may be related to the ability of glucocorticoid to convert precursors to glucose, whereas other agents that protect against hypoglycemia depend largely upon mobilization of glucose from glycogen stores. The presence of chronic, low-grade infections can also cause lability in diabetics, so these conditions should be carefully ruled out.

Patients with labile diabetes mellitus are often young, active persons. They can be benefited to some extent by adjusting their food intake to times of increased exercise or maximum insulin effect, by adjusting their insulin dosage and schedule and by decreasing intake of caffeine, which depletes liver glycogen, but sometimes these measures will not produce adequate control. In such cases, the administration of cortisol, 5 mg four times daily, has been found to stabilize their condition and help prevent hypoglycemia. Because this dosage does not result in hypercortisolism, it does not cause an increase in insulin requirement; on the contrary, it may result in a decrease in insulin dosage. These patients almost invariably have said that they feel better, with more energy and less fatigue, while taking the steroid.

Routine ACTH tests often show evidence of low adrenal reserve in such cases, but in others, ACTH tests may fall within normal limits. It is interesting to note that the incidence of diabetes mellitus in patients with Addison's disease is more than double that for the general clinic population, and recent evidence that both of these conditions may result from autoimmune phenomena probably explains this occurrence.

It has been our policy for a number of years to treat patients with labile diabetes with small doses of cortisol, but the reports of evidence that diabetes mellitus might be a manifestation of an autoimmune process[12,13] raised the question whether other patients with diabetes mellitus might benefit from such therapy. The demonstration that Type I (juvenile) diabetes is associated with antibodies to the beta cells of the pancreas and that Type II (adult) diabetes is associated with antibodies to insulin or to insulin receptors provide a rationale for the beneficial effects of small, physiologic dosages of cortisol in both types, since

cortisol is the only substance normally produced by the body that counteracts autoimmunity. Although the mechanism of action of glucocorticoids in autoimmune processes is only beginning to be understood, the beneficial therapeutic effect of glucocorticoids in patients with autoimmune disorders is well documented.

Another type of diabetic that has shown impressive improvement with physiologic dosages of cortisone acetate or cortisol is the patient with insulin resistance. When such patients are given physiologic dosages of one of these steroids, insulin requirement frequently decreases impressively, and the patients have reported striking improvement in energy and sense of well-being.

REGIONAL ENTERITIS AND ULCERATIVE COLITIS

These are two other clinical conditions in which glucocorticoid therapy has been beneficial, and the demonstration that they may be related to autoimmune phenomena possibly explains this beneficial action. The apprehension associated with the employment of these agents, however, has discouraged their use in many clinics. Yet, numerous patients can be maintained in remission by taking small, physiologic dosages of cortisone acetate or cortisol, whereas an exacerbation occurs if the steroid is discontinued. Dr. Crohn, who originally described regional ileitis and granulomatous colitis and who has seen more than 2,000 cases, states,[14] "My experience is that 90 percent of patients can be managed with medication, diet, and rest, and that only 10 percent require surgery. I give moderate doses of prednisone—usually starting with 15 mg a day and cutting down to 10 mg and then to 5 mg. . . . I have had no problem with serious side effects even with long term therapy." The 5 mg prednisone he administers is equivalent to 20 mg cortisol. Investigation of the use of prolonged maintenance therapy with subreplacement dosages of cortisol in these disorders, therefore, certainly seems warranted.

It is interesting to note that Dr. Crohn further states, "The patients soon learn to adjust their own therapy in accordance with their needs. In the case of fever or acute exacerbation, I give an injection of hydrocortisone sodium succinate. . . ." This adjustment of dosage is consistent with the larger dosage necessary to maintain a patient with adrenal insufficiency in optimum health during periods of increased stress and

is consistent with the principle that because hormone requirements may fluctuate, optimum hormone therapy may require variation in dosage under different circumstances.

MULTIPLE SCLEROSIS

Another autoimmune disorder that has recently been reported to be associated with an abnormality in responsiveness of the HPA axis is multiple sclerosis,[15] but I have had no opportunity to study any patients with this diagnosis. On the basis of our experience, such studies might be helpful.

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Chapter 9

VIRAL INFECTIONS INCLUDING THE COMMON COLD, INFLUENZA, INFECTIOUS MONONUCLEOSIS AND SHINGLES

THE COMMON COLD

Before cortisone became available, patients with chronic adrenal insufficiency were extremely vulnerable to stresses of any kind, and an ordinary respiratory infection often caused an acute collapse that was termed an "adrenal crisis." Patients had to be taken to a hospital and given intravenous saline and glucose as well as a parenteral adrenal cortical extract if that were available. After cortisone and cortisol were introduced, patients with Addison's disease were still cautioned regarding respiratory illness, and they were instructed that upon developing the initial symptoms of a common cold they should increase the dosage of glucocorticoid and phone their physician immediately. Concern regarding the occurrence of respiratory illness in such patients was enhanced by the knowledge that large doses of glucocorticoids could impair resistance to infection while masking the symptoms.[1]

It was, therefore, a finding of some surprise and considerable relief that months and then years passed with these patients consistently reporting that they had either no common colds or only very mild attacks. Most of these patients had no symptoms even suggestive of such disorders, but when symptoms did occur, a prompt increase in the replacement dosage of glucocorticoid was often followed by a disappearance of symptoms without recurrence when the dosage was returned to maintenance levels. During this time, other members of the patients' families seemed to have their usual quota of respiratory illnesses, so the absence of such illness in the patients could not be attributed to lack of exposure to the viruses.

An additional reassuring observation was that when patients with adrenal insufficiency developed respiratory infections, the increase in

dosage of replacement glucocorticoid did not cause an increase in complicating bacterial infections such as sinusitis or bronchitis, and unless a bacterial complication developed, antibiotic therapy was not necessary.

The question naturally was raised whether the patients who apparently experienced shortened or aborted courses were really developing a respiratory illness, but when a number of patients reported the same phenomenon at times when other members of their families were having acute respiratory illnesses, it appeared that the increase in dosage of glucocorticoid at the onset of the infection might be enabling the patient either to ward off or to recover from the infection more quickly. This possibility did not seem too unreasonable, since the development of common colds or other upper respiratory illnesses is often related to a "decrease in resistance" on the part of the host. The various conditions that seem to decrease resistance, such as excessive fatigue, lack of sleep, and emotional upsets, are those that would throw more strain on the hypothalamic-pituitary-adrenal system.

Meanwhile, patients who were receiving physiologic dosages of glucocorticoids for other conditions such as hirsutism or ovarian dysfunction began to report that they seemed to get fewer colds than other members of their families, often escaping completely when everyone else in the family had been ill. Every patient on low dosage glucocorticoid therapy did not report this apparent protective effect, but many did.

The possibility that glucocorticoids might enhance resistance to infection is so contrary to their well-known effect of impairing immunity that it was initially considered with skepticism. Yet, a review of the medical literature reveals an impressive amount of evidence that physiologic amounts of glucocorticoids can have a protective effect against infection. Perla and Marmorston summarized the evidence for this effect prior to 1941,[2] and Beisel and Rapoport summarized this evidence up to 1969.[3]

Both morphologic and physiologic studies point to a significant role of the adrenal glands in the defense mechanism of the body against intoxications and infectious diseases. In the 1920s, Aschoff[4] and Goldzieher[5] described striking morphologic changes in the adrenals in infectious diseases. Infections such as diphtheria, scarlet fever, and every septic condition observed during World War I, including streptococcal infections and infections due to gas bacillus, were associated with marked edema of the adrenal cortex and diffuse regression of lipoid material. Fatal cases of malaria and peritonitis were also reported to have evidence

of degeneration and necrosis in the adrenal cortex, with hemorrhage and arterial thromboses, without similar changes in other organs. Acute hemorrhagic necrosis of the adrenal cortices in some cases of meningitis, so-called Waterhouse-Friderichsen syndrome, was well known, and a less severe but life-threatening reversible adrenal insufficiency has been reported in fulminant meningococcemia.[6]

With evidence that the adrenals may be seriously damaged in the course of severe infections, the question arose whether the cortex or the medulla was primarily involved in resistance to infection. In 1926, Jaffe and Plavska,[7] in studies of susceptibility of adrenalectomized rats to typhoid vaccine, noted that evidence strongly suggested the greater significance of the cortex than of the medulla. Dr. David Marine, who performed classical research on the relationship of iodine deficiency to development of goiter, also studied the relationship of the adrenals to resistance.[8] Ingle[9] confirmed the observation that the cortex was more important in maintaining the resistance of the organism to histamine shock. Hartman and Scott[10] and Perla and Marmorston-Gottesman[11] determined that adrenocortical extract raised the resistance of adrenalectomized rats to typhoid vaccine almost to normal. Pottenger and Pottenger[12] reported that adrenocortical extract injections were beneficial in protecting guinea pigs against experimental tuberculosis infection. These investigators also reported that the administration of adrenocortical extract to tuberculous patients improved their energy and lessened fatigue. Whitehead and Smith[13] reported encouraging results of administration of injections of adrenal cortical extract to patients with severe infections such as typhoid fever, undulant fever, cellulitis, and sinusitis.

In 1941, Kendall reported that as little as 30 mcg of Compound E would protect an adrenalectomized rat against twenty-five minimum lethal doses of typhoid vaccine.[14] In 1954, Benedek and Montgomery[15] reported that patients with rheumatoid arthritis experienced fewer infections during 465 months of cortisone and/or ACTH therapy than during 411 months without such therapy. In 1958, Kass and Finland[16] reported that when adrenalectomized mice maintained with various replacement doses of cortisone were inoculated with pneumococci, survival was greatest in the groups whose maintenance dose most closely approximately normal adrenocortical status. By contrast, mortality increased progressively toward the extremes of either hypo- or hypercortisolism.

In 1960, Spink,[17] in a report of the use of adrenal steroids in patients with infectious diseases, stated, "Judicious use of corticotropin and corticosteroids frequently contributed to immediate improvement in the condition of patients seriously ill with infections and their complications," and "An inventory of the (81) patients treated in this study has revealed no significant ill effects when the steroids were administered for only a few days, even when large doses were used."

In 1969, Beisel and Rapoport,[3] in a comprehensive review of interrelations between adrenocortical functions and infectious illness, stated "that the human host does fare best when his own pituitary-adrenal axis is normally responsive (or when exogenous hormone is given in optimal replacement dose after adrenalectomy) is a conclusion based upon extensive clinical data and well confirmed evidence in laboratory animals." They further stated that "present information suggests that the secretion of all major corticosteroid hormones is stimulated early in the course of acute infectious illness," and that "all available data support the concept that the glucocorticoid increase in the period of early symptoms varies in magnitude with the clinical severity of an infectious illness." It seems unlikely that nature would, at the onset of an infection, cause increased production of a hormone that would impair resistance to infection. It is much more likely that the increased production of glucocorticoid serves to improve resistance in some fashion.

More recent reports provide more direct evidence that these steroids contribute in some fundamental fashion to normal immunity.

Ambrose[18] has presented evidence that a physiologic level of glucocorticoid is essential to the initiation of the immune process. Pierpaoli and Sorkin[19] state that the effect of the thymus upon the development of the immune mechanism appears to be mediated through the adrenals. Shakelford and Feigin,[20] in studies of the susceptibility of mice to pneumococcal infection, found that the longest survival was associated with maximal endogenous corticosterone response.

It is therefore evident that *physiologic* levels of glucocorticoids, in contrast to pharmacologic levels, have a fundamental *favorable* effect upon the body's resistance to infection.

Recent observations in our clinic seem to be pertinent to this point. Because so many patients reported apparent improvement in resistance to common respiratory infections while receiving physiologic subreplacement dosages of cortisone acetate or cortisol, these dosages were

given to patients who had histories of excessive susceptibility to respiratory infections. When they reported dramatic improvement in resistance to such infections, it was decided to study their circulating immune globulin levels, a method of measuring circulating antibodies that had just become available for clinical use. It was found that such patients frequently had relatively low circulating levels of IgM, the component that seems to be a primary factor in early response to viral and bacterial infections; the administration of 5 mg four times daily of cortisone acetate or cortisol was accompanied by a rise not only in circulating levels of IgM, but often also in levels of IgG and IgA (Fig. 6). When the steroid was stopped, levels of immune globulins decreased, and susceptibility to respiratory infections returned. Hence, the improvement in resistance that occurs in such patients appears to be related to an increase in circulating immune globulins, especially IgM.

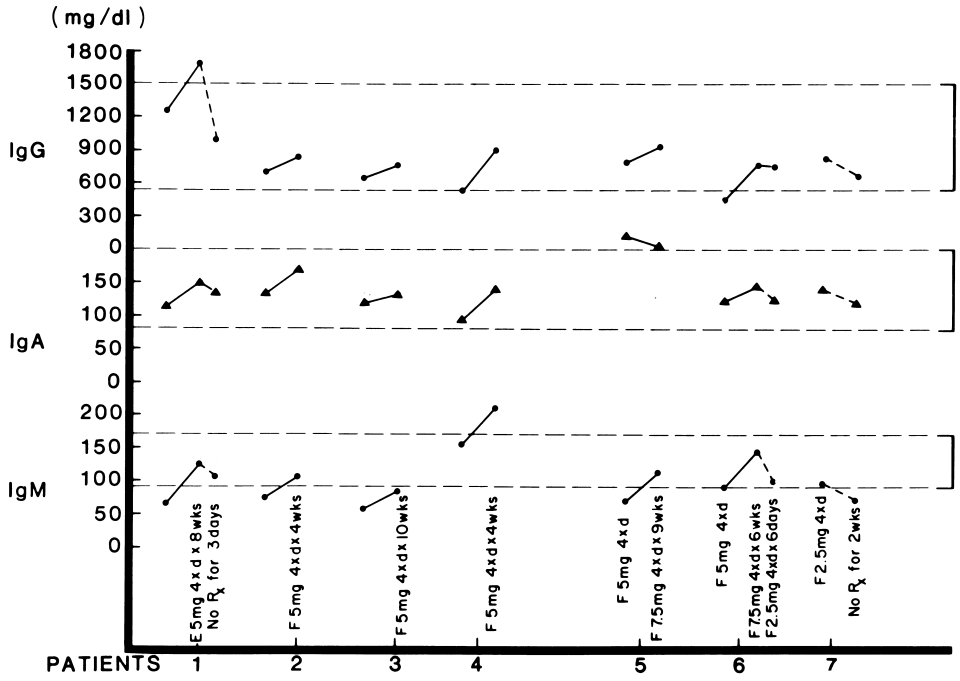

Figure 6. Effects of physiologic dosages of cortisone acetate (E) or cortisol (F) upon circulating levels of IgG, IgA, and IgM. Solid lines indicate effects of an increase in dosage, broken lines indicate effects of decrease in dosage. Horizontal interrupted lines indicate normal ranges for the technique employed.

Several reports over the years have pertained to the effects of ACTH, adrenocortical hormone, and cortisone upon antibody production. Blanchard,[21] in 1934, reported that administration of adrenocortical hormone to intact animals resulted after a period of ten days in a slight rise in opsonic power above the normal level. Fox and Whitehead,[22] in 1935, reported that administration of cortical extract to adult normal rabbits and rats increased the production of hemolysins to sheep red blood cells from 40 percent to 70 percent higher than controls. White,[23] in 1947, reported that cortisone and ACTH have a stimulating effect upon antibody production associated with an increase in the number and activity of phagocytic cells in lymphoid tissue and the dissolution of antibody-containing lymphocytes. Dougherty, Chase, and White[24] reported that administration of ACTH was followed by a rise in circulating antibody. These reports were soon forgotten, however, when numerous reports of the detrimental effect of cortisone and ACTH upon circulating antibody appeared. In retrospect, it seems likely that these discrepancies resulted from differences in dosages of ACTH and cortisone administered to experimental animals, those administered by White and his associates being physiologic, and those administered by others being pharmacologic. This certainly seems to be an explanation for the discrepancy between the report of Levy and Waldman,[25] in 1974, that relatively large dosages of cortisol in mice decreased levels of IgG, IgA, and IgM and our findings that physiologic dosages increased levels of these immune globulins in human subjects.

Identification of components of the immune response such as T-lymphocytes, B-lymphocytes, immunoglobulins, complement, and interferon has been advancing rapidly in recent years, but little is known about the factors that affect these components. Hence, further studies of the effects of physiologic versus pharmacologic dosages of glucocorticoids upon all of the components would be of interest. It appears that the increase in IgM with glucocorticoid therapy occurs chiefly in subjects with low circulating levels of this immune globulin, because subjects with normal levels may not show an increase, and subjects with high levels may even show a decrease during such treatment. Hence, this effect does not appear to be a general stimulatory one but rather to depend upon the initial state of the host.

A review of the evidence for the necessity for physiologic amounts of cortisol for the maintenance of normal immunity was published in 1991[26] and well received by many primary care physicians. It would also

be of interest to determine the relationship, if any, of other components of adrenocortical secretion, such as aldosterone, dehydroepiandrosterone, androstenedione and estrone, to the immune response.

A possible explanation of the contrasting effects of physiologic versus pharmacologic dosages of glucocorticoids upon resistance to respiratory infections, therefore, might be as follows: Normally the body maintains levels of cortisol and immune globulins sufficient to protect against average daily exposure to infection. The lowering of resistance that follows various stresses such as excessive fatigue, lack of sleep, or emotional upset is accompanied by a relative deficiency of cortisol that causes malaise and anorexia, and evidence of infection develops. When the person is able to produce sufficient antibodies and other components of the immune response, the infection subsides and symptoms clear. The mobilization of at least some of the components of the immune response may depend upon the presence of adequate cortisol, since adrenally insufficient subjects are not able to produce a normal immune response. Hence, administration of physiologic dosages of cortisol may help to prevent the lowering of resistance that enables an infection to start or, after an infection has started, may assist the immune response and enable the person to recover more quickly. If, however, an excessive amount of glucocorticoid is present before an infection develops, the immune response may be blocked or misdirected, allowing infections to develop and progress abnormally. It is tempting to speculate that the apparent beneficial effect of vitamin C in the common cold[27] may be mediated at least in part through the adrenals, since the highest concentration of ascorbic acid in the body occurs in the adrenal cortex.

In view of the importance of the common cold as a cause for illness and absenteeism in our economy, intensive studies of the possible protective and therapeutic effects of physiologic doses of glucocorticoids in respiratory and other infections would therefore seem desirable. It is difficult in a clinic such as ours to arrange such a study because patients do not usually report until symptoms have persisted for several days and have failed to respond to home remedies, and they often have bacterial complications by that time.

INFLUENZA

Before cortisone became available, influenza was almost invariably fatal in patients with adrenal insufficiency. As mentioned previously,

therefore, when we were able to prescribe cortisone or cortisol to such patients they were cautioned to increase the dosage at the onset of any infection. After it became evident that optimum maintenance therapy was between 5 mg four times daily of cortisol in patients with mild adrenal insufficiency or low adrenal reserve and 10 mg four times daily for patients who had been totally adrenalectomized, such patients were routinely instructed to double the dosage of glucocorticoids at the first symptoms of onset of respiratory infection, and if they had symptoms suggestive of acute influenza, they were instructed to increase their dosage to at least 20 mg four times daily of cortisol.

When patients followed these instructions, symptoms of fever, generalized aching, acute malaise, and anorexia often cleared within twenty-four hours, and they were able to return to work within forty-eight hours. The dosage was then gradually tapered to their maintenance dosage over the next week, and no recurrence developed, nor were there evidences of complicating bacterial infections.

The impressive improvement of these patients with steroid therapy, plus the similarity between symptoms of acute influenza and those of acute adrenal insufficiency, led to a decision to study plasma cortisol levels in this disease. During the epidemic of influenza in the Cleveland area in March 1976, with the assistance of Dr. José Rivera, a primary care physician in our clinic, plasma cortisol levels were obtained on patients presenting in the acute stages of the illness. When these were found to be remarkably low, ACTH was administered to determine whether the low values were due to adrenal insufficiency. Normal responses to ACTH indicated that the adrenals were not at fault and that the defect lay in the pituitary or the hypothalamus. Furthermore, the administration of cortisol, 20 mg by mouth four times daily, resulted in dramatic improvement.

Viral studies were not available in our laboratory, but Dr. Stephen Mostow agreed to study viral antibody titers on four of our patients. Two patients showed a diagnostic rise in antibody titer confirming influenza A infection; the other two had elevated titers at the time the initial blood specimen was drawn, so they could only be designated as probably acute influenza A infection. Journal editors did not consider this evidence sufficient to be acceptable for publication, possibly because of the bad reputation of glucocorticoids in infections.

The results of these preliminary studies appear in Figure 7. ACTH tests in the four patients with influenza are contrasted with similar tests performed on patients with acute bacterial pharyngitis and tonsillitis.

With the technique employed, a normal unstressed subject usually has plasma cortisol levels between 18 and 32 mcg/100 ml at 8 AM and between 6 and 12 mcg/100 ml at 5 PM. The three patients with clinical influenza whose tests were performed in the morning had baseline plasma cortisol levels of only 5.8, 6.9, and 12.8 mcg, respectively, all much lower than the expected normal level in the unstressed state and relatively even lower compared with the expected level during the stress of an acute infection. These tests were run on the third or fourth day of their illness, at the time they first presented themselves in the clinic for therapy.

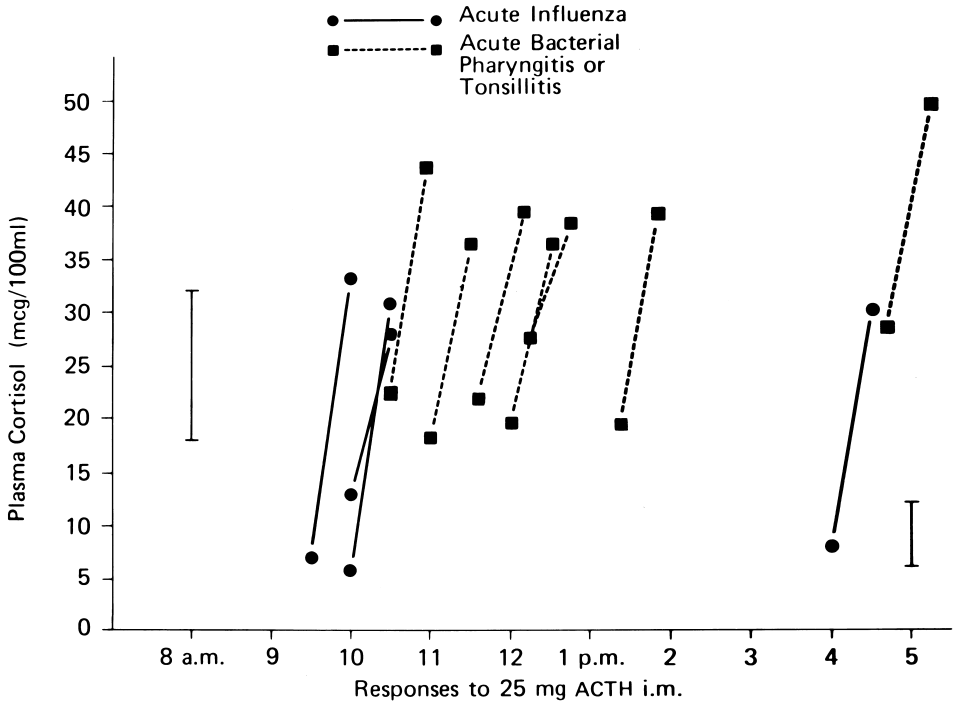

Figure 7. Plasma cortisol levels before and 30 minutes after an intramuscular injection of 25 units of cosyntropin (ACTH) in patients with acute influenza and in patients with acute bacterial pharyngitis or tonsillitis. The bars above 8 AM and 5 PM indicate the usual range of normal plasma cortisol levels for these times of day. Pre- and post-ACTH levels of patients are connected by lines to facilitate comparison.

The degree of lowering seemed to correlate with the severity of the illness, the lowest plasma cortisol occurring in the patient with the highest fever and the lowest white count, and the highest plasma cortisol occurring in the patient with the lowest fever. The baseline level of the patient tested in the afternoon was in the same low range, 8.0 mcg/100 ml. Due to diurnal variation, this was within normal limits for an unstressed subject at this time of day but low for a patient under the stress of an acute infection. The plasma cortisol levels of all four patients responded to ACTH stimulation with an increase well within normal range.

By contrast, the baseline plasma cortisol levels in all seven instances of acute bacterial pharyngitis or tonsillitis were between 18.1 and 25.5 mcg in both morning and afternoon. The plasma cortisol levels of these patients also responded normally to ACTH. Hence, the baseline plasma cortisol levels in patients with acute clinical influenza were impressively lower than the levels of those with acute bacterial pharyngitis or tonsillitis regardless of the time of day. The rise in plasma cortisol levels after ACTH stimulation indicated that the low baseline levels were not due to inability of the adrenals to respond. Because diurnal variation in plasma cortisol levels is known to result from the stimulation of the adrenals by endogenous ACTH, the baseline plasma cortisol levels of the patients with acute influenza were therefore similar to those that would be expected in hypopituitarism. Such findings could be due to an impaired hypothalamic-pituitary response with a decreased production of ACTH, to increased utilization of cortisol associated with the infection, or to a combination of the two.

As a result of these findings, it was decided to treat patients with acute influenza in the same manner in which patients with chronic adrenal insufficiency were treated when they developed acute infections. Cortisol, 20 mg by mouth four times daily before meals and at bedtime, was started. Patients were instructed to continue this dosage until they felt well, then decrease to 10 mg four times daily for two days, then 5 mg four times daily for two days, then stop. Because of initial concern regarding the possibility of complicating bacterial infection, the first three patients with influenza were also given antibiotics (erythromycin or penicillin) for seven days, but subsequent patients have received cortisol without antibiotics. Supplementary multiple vitamins were also administered. Because the epidemic subsided, a total of only seven cases were treated in this manner.

Clinical responses were striking. Within twenty-four hours all patients felt much better, and within forty-eight hours symptoms such as fever, malaise, and generalized aching had completely subsided, and they felt quite well. The initial dosage of cortisol was decreased after forty-eight hours and discontinued after six days of therapy. No relapses or complications occurred.

Although most fatalities occur in older patients with complicating illness that could impair resistance to any infection, at least a small percentage of deaths in influenza epidemics occur in young, apparently healthy persons,[28] suggesting an impairment of their defense response. In a pathologic report of nine cases who succumbed to influenza in the 1957 epidemic in England, all of whom were previously healthy and eight of whom were young, Roberts[29] commented on the paucity of cellular reaction in the bronchi and lungs, which were the sites of overwhelming congestion and loss of epithelium. He stated that this "apparent lack of response might be ascribed either to a depression of the tissue reaction by the virus or to overwhelming of the host by the staphylococcal infection before a tissue response could occur." He further stated that "in none of the (nine) cases was there any evidence of suprarenal damage." Because overwhelming infections characteristically cause intense stimulation of the adrenals, such pathologic findings suggest a lack of usual adrenal stimulation in response to stress.

The suggestive evidence that the impairment of response may be located at the level of the pituitary or hypothalamus has interesting implications. In view of the known effect of viruses upon formation of cellular proteins, and because both pituitary and hypothalamic hormones are protein in nature, in contrast to adrenal cortical hormones, which are steroids, it is possible that the influenza virus in some way interferes with the production of adrenocorticotropic hormone by the pituitary or of corticotropin releasing factor by the hypothalamus. Studies to answer this question, as well as the question of whether other anterior pituitary or hypothalamic hormones are affected, would, therefore, be of interest.

Why the virus appears to have more devastating effects upon some patients, even among those apparently healthy, also remains to be determined. It is evident that most patients cope with this alarming potential of the virus and recover within seven to fourteen days. Probably factors such as the virulence of the infecting agent, the size of the

inoculum, and the state of resistance of the host at the time the infection develops contribute to the clinical severity.

A review of the literature revealed that in the influenza epidemic of 1958 in London, Mickerson[30] had reached similar conclusions regarding impaired pituitary response as a result of studies on four cases. At that time plasma cortisol levels were not available, but urinary excretion of 17-ketosteroids and corticoids before and after a three-day course of intramuscular corticotropin, 40 units daily, revealed that in each case urinary steroid excretion was subnormal but increased after ACTH administration. He further reported that clinical improvement occurred in all four patients after the three-day course of intramuscular ACTH. In one case, no further treatment was required. In the other three cases, symptoms recurred after ACTH was discontinued, so they were given prednisolone, 5 mg three times daily for one day, followed by 2.5 mg three times daily for periods ranging from two to three weeks, with uneventful recoveries. For the first five days of hospitalization, each patient was given penicillin prophylactically. He also noted that in autopsy reports of patients dying with acute influenza, evidence of adrenal damage was uncommon. In twenty-four necropsies of fatal influenza reported by the Public Health Laboratory Service in 1958,[31] adrenal hemorrhage was noted in only eight cases. Mickerson interpreted his observations as indicating evidence of reduced anterior pituitary activity in acute influenza.

Observations of Skänse and Miörner[32] were also interesting. In a report of the presence of preexisting untreated adrenal insufficiency in at least four and possibly five patients who succumbed to influenza in Malmö, Sweden in 1957, they noted that "resistance in Asian influenza appears to be lowered more by untreated adrenocortical insufficiency than by chronic cardiac or renal disease." They further noted that other patients with adrenal insufficiency receiving adequate substitution therapy tolerated an attack of influenza as well as, *or better than*, patients with normal adrenals. They concluded that "in all cases of severe influenza any suspected adrenal insufficiency should be compensated."

For many years it has been recognized that the clinical symptoms of acute malaise, anorexia, fever, weakness, exhaustion, and generalized aching that occur with any acute severe infection, but especially with influenza, are similar to the symptoms of acute adrenal insufficiency. It has also been known since the early days of cortisone therapy that

administration of ACTH in suitable dosages to patients with acute infections such as pneumonia produced a dramatic improvement in these symptoms. The patients no longer felt ill, but the pathologic effects of the bacteria in the lungs persisted and might even progress if antibiotic therapy was not started.[1] This caused such alarm that the use of ACTH or cortisone in the treatment of pneumonia was soon abandoned, even though patients receiving either of these hormones plus antibiotics seemed to recover nicely. The observations in our patients and in those of Mickerson strongly suggest that, in the case of influenza at least, such symptoms are actually due to inadequate adrenal response secondary to interference with hypothalamic or pituitary function. The possibility that a relative deficiency of adrenal response might be present in the incipient phase of any infectious disease should therefore be further investigated.

The response to treatment with physiologic dosages of cortisol in our cases in 1976 was impressive, and the absence of complications was encouraging.

It should also be remembered that the cases were chosen for our study because they had uncomplicated influenza. Secondary pneumonias due to *H. influenzae,* streptococci, staphylococci, or other pathogenic bacteria are common complications of the viral infection, so if any suggestion of such complicating bacterial infections occurs, suitable antibiotic therapy in addition to the steroid therapy should be instituted promptly. It is, therefore, advisable to perform throat cultures as well as differential white blood counts and baseline plasma cortisol levels on every patient at the time of the initial visit and to perform chest x-rays on any patient who has symptoms or signs suggestive of pulmonary involvement.

If the plasma cortisol level is relatively low, supplementary cortisol in dosages comparable to those used in this study may be dramatically helpful, and if there is any question regarding the possible presence of complicating bacterial infection, antibiotic therapy should be started. Patients with influenza plus a bacterial infection usually still have a relative leukopenia but with a preponderance of neutrophiles and a shift to the left in contrast to uncomplicated influenza. With such combined therapy, it is possible that the incidence of severe and fatal complications of influenza can be lessened or prevented.

These observations raise the question whether this type of response is unique for the influenza virus or whether it may occur in varying degrees

with other viral illnesses. Evidence that it may occur in patients with infectious mononucleosis will be discussed. Absence of leukocytosis is characteristic, not just of influenza, but of all virus infections. This could be due at least partly to a lack of normal cortisol response to stress, since cortisol stimulates a granulocytic leukocytosis. The degree of lowering actually suggests a suppression of granulocytes as well. Evidence has been reported that influenza virus inhibits chemotaxis of polymorphonuclear leukocytes and monocytes,[37,38] so this effect probably contributes to the absence of leukocytosis.

No report of influenza would be complete without mentioning the terrible influenza epidemic of 1918. The 1918 flu epidemic was a terrifying occurrence towards the close of World War I, killing more Americans in a single year than were killed in battle in World War I and World War II plus the Korean War and the Vietnam War combined!

Gina Kolata has written an excellent book published in 1999 entitled *Flu: The Story of the Great Influenza Epidemic of 1918 and the Search for the Virus That Caused It.*[39] Yet this virus has never been identified! Influenza viruses return every year, but none with the vicious behavior seen and recorded in the 1918 epidemic!

In those days, the ability to type and study viruses had not been achieved, but it was obvious that this disease had behaved differently from any described previously or subsequently.

It was first reported to have occurred in army barracks at Fort Devens, Massachusetts, about 20 miles west of Boston, where 150 or more healthy young men were crowded into barracks designed to house 100 men.[40] Some had to share their beds with another soldier; others had to sleep on cots or even on the floor. At that time, Fort Devens contained about 50,000 men, or did before the epidemic developed!

After the men became ill and were admitted to the hospital, within a few hours they developed cyanosis so that it was difficult to distinguish the white men from the colored men, and they often died within 24 hours, averaging about 100 deaths per day![41]

The Surgeon General sent Dr. William Henry Welch, a prominent internist, with three other excellent internists to determine what was going on. Dr. Welch had been a president of the American Medical Association in addition to other honors. The others in his group included Colonel Victor C. Vaughn, who also had been a president of the American Medical Association, Dr. Rufus Cole, President of the Rockefeller Institute, and Dr. Simeon Walbach of Harvard Medical School.

These outstanding physicians were horrified by what they found in the autopsy room. When Dr. Welch opened the chest of one of the young men, he found the lungs were "blue and swollen, with wet, foamy surfaces and little real consolidation," and he said, "This must be some new kind of infection." These autopsy findings were characteristic of those of soldiers dying in the crowded barracks at Fort Devens, and of other soldiers who had similar crowded barracks at Camp Lupton on Long Island near New York City[41], but others who developed flu at home or in hospitals had a more typical illness, varying from mild to severe or fatal, but without the vicious aspects seen at Fort Devens and Camp Lupton.

This vicious type of influenza was also reported to have occurred in Eskimo igloos in Alaska[42], where a number of people who had crowded into a small church for services and a dinner later developed influenza and died within a few days.

There is a factor common to these infections that might promote this vicious behavior of the influenza virus: crowding! This is most apparent in army barracks where 150 or even 200 men were crowded into barracks constructed for 100 men, but it also might explain the outbreak of vicious flu in igloos in Alaska.

Under certain conditions of crowding where a number of people are in a closed space rebreathing their own expired air as well as that of others, such as in the army barracks at Fort Devens and at Camp Lupton, or in igloos in Alaska, the virulence of the influenza virus might increase so greatly that it directly attacks the tissues of the lungs of its hosts causing their lung tissues to become filled with fluid so that they literally drown in their own pulmonary secretions!

If this explanation is correct, studies of this effect might be quite hazardous and would require special precautions, using laboratory animals instead of human subjects! Patients with influenza should also be advised to have plenty of fresh air in their rooms!

But this is not the effect of influenza viruses in patients in rooms with varying amounts of fresh air described in the 1918 epidemic by Ms. Kolata. Patients under these conditions might have varying degrees of severity of their illnesses, probably depending upon the amount of fresh air in their bedrooms as well as upon the virulence of the virus itself. Patients with relatively large amounts of fresh air in their rooms might have a relatively mild illness, whereas those with less fresh air might have a more severe or even fatal illness, but the fatalities would be associated with a more typical type of pneumonia.

In the months of January to March 1995, and January to March 1996, with the help of Dr. Jack M. Gwaltney, Jr., and his associates Dr. James C. Turner and Dr. Monica Lobo, we were able to study the effects of influenza virus, type H3N2, in 18 young adults (Fig. 8 and Fig. 9). These studies clearly indicated that the influenza virus attacks the human body by impairing the production of adrenocorticotropic hormone (ACTH) by the pituitary gland thereby impairing the production of cortisol.

These observations confirm the observations made by Dr. Rivera and me in the influenza epidemic of 1976 in the Cleveland area, in which we reported that studies on four patients with acute influenza indicated that the influenza virus attacks the human body by impairing the production of ACTH, but journal editors at that time considered these results insufficient evidence for publication.

We now know that influenza viruses attack the human body by decreasing the production of adrenocorticotropic hormone (ACTH)[43], thereby decreasing the production of cortisol, the only hormone that is absolutely essential for life, so treatment with physiologic dosages of

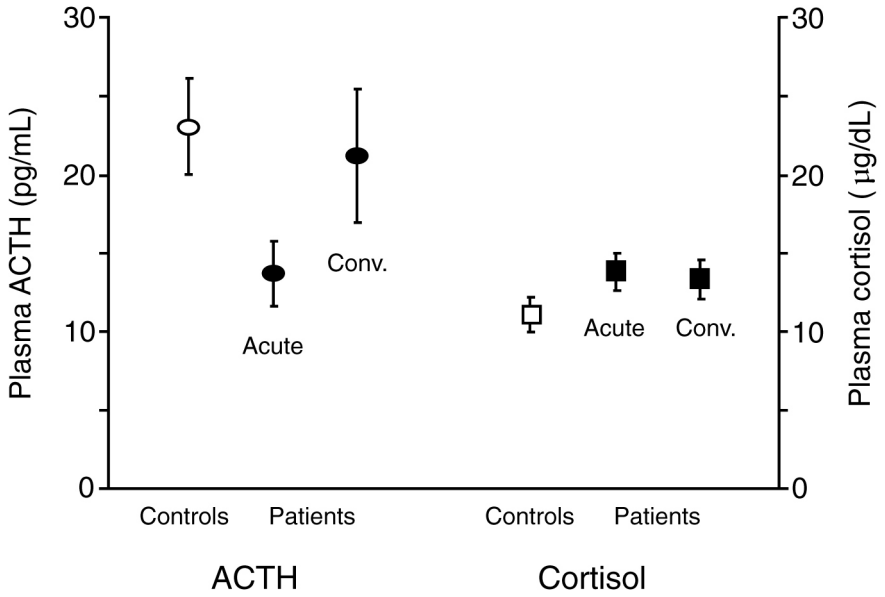

Figure 8. Mean plasma adrenocorticotropic hormone (ACTH) and cortisol levels ± SE in 19 patients with acute and convalescent influenza virus type A infection (closed symbols) and in 11 controls (open symbols). Conv. = convalescent.

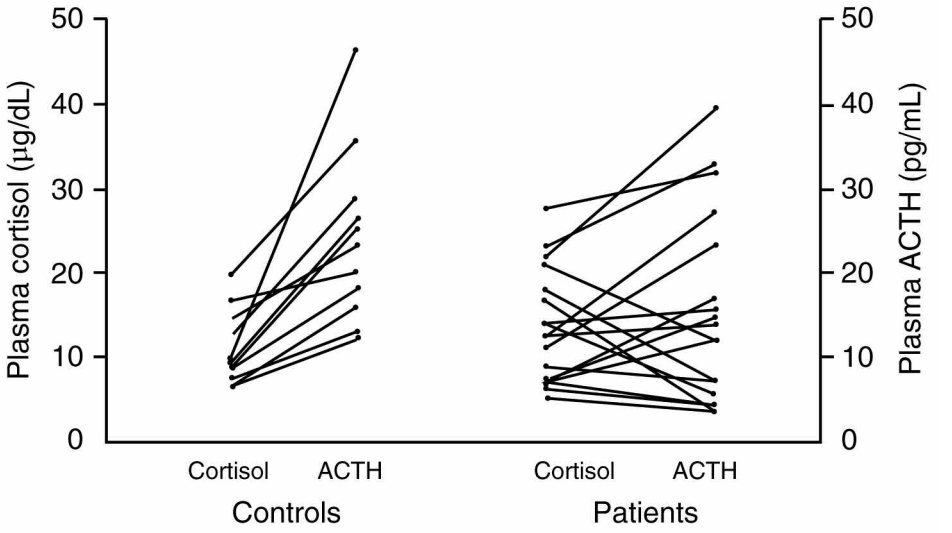

Figure 9. Plasma cortisol and adrenocorticotropic hormone (ACTH) levels in paired samples from 19 patients wth acute influenza A and in those from 11 controls. (Two patients had the same levels: cortisol, 8 µg/dL; ACTH, <5 pg/mL.)

cortisol is a safe and beneficial therapy for patients with influenza, regardless of its type.

An interesting recent development has been reported in the news media of an apparently new respiratory disease in China labeled SARS (Severe Acute Respiratory Syndrome) that has been spreading over the past six months. Because we now know that the common cold and influenza are associated with a deficiency of cortisol, it would be interesting to determine whether SARS is also associated with cortisol deficiency, in which case treatment with safe, physiologic dosages of cortisol should be helpful.

Meanwhile, it must be remembered that excessive doses of any glucocorticoid, including cortisol or cortisone acetate, can impair resistance to infection as well as cause other hazardous side effects, so the indiscriminate use of these agents in infectious disease should never be undertaken.

INFECTIOUS MONONUCLEOSIS

The history of the use of physiologic dosages of glucocorticoids in infectious mononucleosis is an interesting story, demonstrating problems

that have arisen as a result of the bad reputation of these agents. In 1962, Chappel[44] reported beneficial effects of cortisone therapy in 111 cases of infectious mononucleosis, including control of symptoms within a few days and elimination of long periods of bed rest and disability. Other clinicians have confirmed these beneficial effects in infectious mononucleosis with other glucocorticoids. In a study of sixty-six students with severe but uncomplicated infectious mononucleosis, Bender[45] reported that treatment with ACTH or prednisolone produced significant shortening of illness and loss of time from classes compared with matched controls. Practically all of these reports came from student health centers at universities where infectious mononucleosis is frequently encountered. Academic medical research centers, however, have been hesitant to accept these results, and medical texts recommend that glucocorticoid therapy in infectious mononucleosis be reserved for patients with more severe illness or complications. Because the clinical reports indicate that glucocorticoid therapy in dosages recommended helps to prevent such severe illness or complications, and because there has been no indication that patients with infectious mononucleosis treated with glucocorticoid therapy in the doses recommended develop any of the hazardous side effects that are so dreaded, a reconsideration of the current recommended treatment of infectious mononucleosis seems advisable.

We have also observed the impressive beneficial effects of physiological dosages of cortisone or cortisol in patients with acute infectious mononucleosis. Because patients with adrenal insufficiency who develop acute infections with fever and malaise require doses of 20 mg four times daily of cortisol, we have administered similar dosages until patients felt well, which was usually within forty-eight hours. Subsequently, the dosage has been tapered to 10 mg four times daily for two days, then to 5 mg four times daily for a week, before it is discontinued altogether.

After we found that plasma cortisol levels were low in acute influenza, ACTH tests were performed on patients with acute infectious mononucleosis. The results were similar to those encountered in patients with acute influenza, but the depression of plasma cortisol levels was less severe. In the initial twenty-four hours of the illness, plasma cortisol levels tend to be within normal limits, but subsequently they tend to be low. Because they respond to ACTH with a normal rise, it is evident that there is no primary impairment of adrenal cortical function, and the

impression again occurs that the virus is interfering with hypothalamic or pituitary response to the stress.

These observations may be related to evidence that cell-mediated immunity is impaired during acute infectious mononucleosis[46] and suggest that the effect of physiologic versus pharmacologic dosages of glucocorticoids upon cell-mediated immunity should be studied further.

SHINGLES (HERPES ZOSTER)

Another viral infection that has been reported to be helped by administration of glucocorticoids, at least in some cases, is shingles or herpes zoster. This produces a relatively common and sometimes severe and debilitating illness in older individuals that may persist for months. Although my experience with treatment of this illness is limited, one of our patients developed this disorder while taking physiologic dosages of cortisol for mild adrenal deficiency. A course of acyclovir for seven days did not seem to affect the symptoms or rash around the lower anterior and posterior chest wall, but an increase from his maintenance dosage of cortisol of 5 mg four times daily to 20 mg four times daily enabled him to continue normal daily activities except for a few days when a dosage of 25 or 30 mg four times daily seemed to be necessary. While he was taking 20 mg cortisol four times daily his plasma cortisol at 2 PM, six hours after his last dose of cortisol, was 12 μg/dl, and 4 days later, while he was taking 25 mg cortisol four times daily, his plasma cortisol at 2 PM was 16 μg/dl, both values well within normal range for an unstressed person taking no medication and consistent with Ingle's impression that the increased production of cortisol that occurs during stress is merely maintaining a normal physiologic level of cortisol in the body, and not producing hypercortisolism.[47] The patient's increased dosage of cortisol could be tapered back to his maintenance dosage 6 weeks after the onset of shingles without further symptoms or evidence of recurrence. Further studies of adrenocortical function and the possible benefit of physiologic dosages of cortisol in patients with this viral disorder might therefore be helpful.

POSTVIRAL SYNDROME

A few patients, after acute infections with influenza, infectious mononucleosis, or infectious hepatitis, have persistent symptoms of

malaise, easy fatigue, and general debility lasting for several weeks to several months. After chronic fatigue from other causes was found to be frequently associated with a state of low adrenal reserve or mild secondary adrenocortical deficiency, and after patients with acute influenza or infectious mononucleosis were found to have relatively low levels of plasma cortisol, ACTH tests were run on patients with the postviral syndrome. In almost every case, patients were found to have either low adrenal reserve or a low baseline plasma cortisol level, suggesting inadequate pituitary stimulation. In some patients, persistently elevated viral antibody titers suggested a chronic viral infection.

When cortisone acetate or cortisol, 5 mg four times daily, was given to these patients, impressive improvement in symptoms resulted. Further studies are necessary to determine why some patients develop these complications whereas others do not, but it is evident that under some circumstances viral infections can produce a persistent impairment of the pituitary-adrenal response to stress for several months and that in such cases the administration of small, physiologic dosages of cortisol will produce symptomatic benefit without apparent harm.

OTHER INFECTIONS

The observations of Kass, Ingbar, and Finland[1] that cortisone can counteract the symptoms of pneumonia; of Smadel[48] and Woodward[49] and their associates that cortisone, when given in conjunction with chloramphenicol, greatly improved the clinical course of patients with typhoid fever; and of Spink[17] that glucocorticoids can improve the symptomatology and shorten the course of other severe infections all suggest that physiologic dosages of cortisol or cortisone acetate might be beneficial in any severe infection, at least in its early stages. The administration of cortisone with suitable antibiotic therapy has even been reported to be helpful in tuberculosis.[50] It is apparent that in any bacterial infection, glucocorticoid therapy will not replace antibiotics and, hence, glucocorticoids should be given in conjunction with appropriate antibiotics.

A number of other reports of therapeutic trials of glucocorticoids in severe infections and septic shock have appeared, and these have been summarized and criticized by Weitzman and Berger.[51] They pointed out deficiencies in adherence to standards of clinical trial design in many of these studies, including failure to follow double-blind procedure.

Unfortunately, the use of double-blind procedures in studies of hormone effects is not valid unless one is studying clinical conditions where one dosage of the hormone for one duration of administration is optimum, and such conditions seldom, if ever, occur, especially in patients with severe infections.

SUMMARY

During the past 21 years since this book was first published, much has been learned about response to infection through activation of the HPA axis and its various components, but little attention has been paid to the importance of normal adrenocortical function in achieving its goal of protecting the health of the individual. The suggestive evidence that supplementation with small, physiologic dosages of cortisol that are not sufficient to raise blood levels above normal enhance resistance (immunity) to common respiratory viruses in patients with mild adrenocortical deficiency suggests that an adequate amount of cortisol is necessary to provide protection against common respiratory infections and that viruses may gain access to the body by interfering with this defense mechanism. Viruses are obviously parasites, so they must gain access to living tissues in order to propagate, but normal immunity is usually sufficient to prevent their intrusion. Hence, they must await an opportunity to invade at a time when resistance is lowered, possibly by stresses such as excessive fatigue or inadequate sleep or dietary indiscretion, in order to gain access to living tissues and multiply, thereby causing illness such as the common cold.

Other viruses, such as those causing influenza, devise ways of changing their coating in order to bypass the defenses of the immune system of their potential hosts, but the influenza virus goes a step further by interfering with the normal HPA response, impairing the production of ACTH by the pituitary and thereby impairing the increased production of cortisol that characterizes the normal HPA response to infection. In major epidemics, this interference with the HPA response apparently enables the virus to cause severe and even fatal illness in some patients. Although much more has been learned about the factors contributing to this alarming potential, the ability to provide adequate cortisol in the early stages of such infections may not only speed recovery, but also avoid complications and even be life-saving. However, here an extremely

important word of caution is necessary: If an *excessive* amount of cortisol or any other glucocorticoid is given *before* a challenge to the immune system occurs, this may block or interfere with a normal HPA response with disastrous results (see Schwartzman phenomenon, Chapter 11). Hence, larger dosages of cortisol or any other glucocorticoid should not be given capriciously, but only when clearly indicated and in proper amounts. Failure to understand this is a major cause for the bad reputation that glucocorticoid therapy has achieved.

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Chapter 10

MISCELLANEOUS CLINICAL CONDITIONS INCLUDING FUNCTIONAL HYPOGLYCEMIA AND THE CHRONIC FATIGUE SYNDROME

In previous chapters clinical uses of physiologic dosages of cortisol or cortisone acetate in conditions in which their use has been either established or indicated for logical reasons have been discussed. I would now like to discuss other conditions in which, for various reasons, therapeutic promise also seems likely. In some of these conditions, the rationale for their use is also logical, but in others, at first glance, their use would seem contraindicated, at least on the basis of popular understanding of their actions.

HIRSUTISM

Although racial and familial factors contribute to the sensitivity of hair follicles to stimulation, the source of stimulation of coarse hair growth on the face, body and extremities is androgen. This is produced normally by the adrenals and testes and, under certain abnormal circumstances, by the ovaries. In addition, other tissues may be capable of converting precursors to androgens.

In a study of fourteen patients with hirsutism, Gibson and his associates[1] found evidence of abnormality of adrenal response to ACTH in all except three. In five patients, evidence suggested a partial deficiency of 3ß-hydroxysteroid dehydrogenase? 4–5 isomerase and in five others a partial deficiency of 11ß-hydroxylase. Also, in six patients an abnormally high increment of dehydroepiandrosterone relative to hydrocortisone was noted. Hence, patients with hirsutism as well as those with ovarian dysfunction have a high incidence of abnormal adrenal steroid metabolism.

Androgen excess causes increased hair growth on the beard area, trunk, and extremities and a thinning of scalp hair. Evidence of excessive

androgen production is manifested by increased urinary excretion of 17-KS or by elevated plasma levels of testosterone or of DHEA sulfate.

Women with complaints of hirsutism or thinning of scalp hair will often be helped by the administration of small, subreplacement dosages of cortisol, suggesting that the hirsutism and/or thinning of scalp hair results from a pathologic process similar to that which causes congenital adrenal hyperplasia, or by some autoimmune disorder. In some cases, plasma ACTH may be elevated prior to treatment. Improvement is slow in becoming evident, however, apparently due to the property of hair follicles that causes them, once they have produced coarse hairs, to continue to grow coarse hairs until they are replaced by fine ones. Because hairs are replaced at intervals of up to eighteen months, a patient may have to continue treatment for a year or more before appreciable improvement is noted. Also, unless the dosage of cortisol is increased during periods of stress, the production of androgen at those times of increased adrenal activity may be sufficient to maintain the hirsutism. Furthermore, the excessive production of androgen must be suppressed throughout the twenty-four hour period, so care must be taken to have a maximum interval of 8 hours between doses of cortisol and the dosage must be increased temporarily during times of increased stress. The impressive difference in androgen excretion between a daily dosage of 10 mg cortisol administered as 5 mg every twelve hours versus 2.5 mg four times daily was shown in Figure 4 (see page 61).

If treatment is continued regularly for eighteen months or longer, most patients will note some diminution of excessive hair growth and some return of thinned scalp hair, but beneficial effects are seldom dramatic. It is my impression that patients who have received the greatest benefit have been those who have followed instructions regarding therapy most carefully. It is difficult for many patients to appreciate the necessity of taking medication regularly, especially for a condition as benign as hirsutism, so they often forget doses or fail to increase doses during infections or other acute stresses.

Some patients appear to have excess androgen from the ovaries or from both the ovaries and adrenals.[2–4] In such cases, the pathologic physiology appears to involve a relative deficiency of an enzyme in the pathway of production of estrogen that results in an excessive production of androgenic precursors, and an elevated level of follicle-stimulating hormone (FSH) in the blood or urine may be helpful in indicating

their source. The administration of small, physiologic doses of estrogens, such as 0.3 mg estrone sulfate daily except during menses, will help in correcting the disorder, but again it is necessary to continue treatment for a year or longer before improvement becomes manifest. In patients with disorders of both the adrenals and ovaries, such as the Stein-Leventhal syndrome,[5] both cortisol and estrogen must be given simultaneously. If the woman needs estrogen, it will not interfere with the regularity of her menstrual cycles; on the contrary, it will make them more normal, in contrast to women who do not need estrogen, whose ovulations may be delayed and cycles prolonged by such estrogen administration.

Recently there has been concern expressed regarding the safety of estrogen therapy due to statistical evidence that women given estrogens at the menopause had a higher incidence of endometrial cancer than those who received no estrogen. It was feared that the estrogen therapy might have in some way contributed to the development of cancer.

It is unlikely that physiologic dosages of a normal hormone would cause cancer. If they did, the highest incidence of cancer of the endometrium would be in young women because they have the highest physiologic levels of estrogen. It is not surprising that estrogen administration at the menopause is associated with a statistically higher incidence of carcinoma of the uterus or breast, because these tissues are dependent upon estrogen for their normal development, but in such cases estrogen would merely be a permissive factor, not a causative factor. It is unfortunate that this distinction has not been publicized, because many women with estrogen deficiency, especially young women, are being frightened from taking a hormone that they need for normal development and health. Synthetic estrogens such as diethylstilbestrol, on the other hand, introduce proven potential hazards, so they are contraindicated at any time.

In my experience with administration of physiologic dosages of normal estrogens such as conjugated estrogens, ethinyl estradiol, and 17-beta-estradiol, no untoward effects have been encountered. They are routinely administered on a cyclic schedule. Replacement dosages are taken for three weeks, then omitted for a week. Subreplacement dosages, on the other hand, are usually prescribed to promote more normal ovulatory cycles, so they are taken until menses start, then omitted until menses stop. The nausea that has been reported with estrogen therapy apparently results from larger doses, as patients treated as described have not complained of nausea.

There is evidence that androgen can be produced from precursor steroids in peripheral tissues, and this is thought to cause hirsutism in some cases. If it does, it must be either under ACTH or FSH control or a manifestation of an autoimmune process, because in every case of hirsutism I have been able to study, the excessive levels of androgen in the blood or urine or the hirsutism itself have improved with the administration of cortisol or cortisone acetate, or estrogen or a combination of one of the former with the latter.

Case 1 is that of a woman who presented with a problem of hirsutism and who has been followed for thirty years.

Case 1

The patient was referred in 1950 at the age of twenty-two because of increased hair growth on her chin, which had been noted for about a year. For several months, she used a depilatory, but it seemed to be getting worse, so she consulted a dermatologist, who started electrolysis. Her health had otherwise been good. The menarche had occurred at age twelve and cycles had been regular, with intervals of thirty days, menses lasting four days. Family history was negative for endocrine disorder. Physical examination was normal except for slight increase in hair growth on the chin, periareolar and subumbilical areas, and mild acne of the chin. The clitoris was not enlarged. Urinary 17-KS were in the high normal range. The patient was assured that there was no evidence of endocrine tumor, but no other treatment was known at the time.

She returned five years later with evidence of progression of hair growth to include moderately severe hirsutism of the face, chest, periareolar and subumbilical areas, and legs. She also had moderate acne of the chin and shoulders. During the previous six months, she had missed one menstrual period, and another had occurred after an interval of six weeks. Breast development was at the lower limit of normal. Urinary 17-KS were 24.6 mg/24 hours, and a repeat determination was 24.0 mg/24 hours.

Because of the slow progression, it was thought likely that she had a functional disorder of adrenal steroid metabolism, so she was given cortisol, 5 mg every eight hours. A month later, urinary 17-KS were 11.0 mg/24 hours, consistent with the impression that this was a case of functional steroid disorder rather than a tumor. Six months later, there was definite evidence of decrease in hair growth with softening of the texture of the hairs. The dosage of cortisol was increased to 5 mg four times daily, and this resulted in a decrease in urinary 17-KS to 7.5 mg/24 hours. She continued to take cortisol, 5 mg four times daily, until 1967, when cortisone acetate, 5 mg four times daily, was substituted. In 1970, the dosage was decreased to 2.5 mg four times daily for eighteen months, but she developed eczema, so the dosage was returned to 5 mg four times daily. This has been continued up to the present, the eczema having subsided except for occasional mild occurrences.

During her treatment, the patient was married and had three full-term pregnancies. Excessive hair gradually improved so that she had to pluck only an occasional coarse hair from her chin, and her complexion remained clear. In 1975, after the patient had taken physiologic dosages of cortisol or cortisone acetate for eighteen years, an ACTH test showed a baseline plasma cortisol of 15 μg% at 12 noon and an increase to 27.9 μg% thirty minutes after an I.M. injection of 25 units of Cortrosyn. Plasma testosterone while taking cortisone acetate, 5 mg four times daily, was 25 ng/dl, well within normal range.

This case demonstrates not only the effectiveness of small dosages of cortisol or cortisone in patients with hirsutism, acne and ovarian dysfunction provided they are taken regularly, but also their safety over the period of thirty years that this patient was followed, including three normal pregnancies.

Case 2 was referred primarily for excessive hair growth, but she also had other problems related to a mild hormonal disorder.

Case 2

This young woman was referred at the age of twenty-two years. She had noted some dark hair on her face and body in childhood, but this had become progressively worse since the menarche at age fifteen. Her cycles had been irregular, with intervals of two to eight weeks, menses lasting four to five days with clots and cramps on the first day. Her gynecologist had given her an oral contraceptive for three months, and subsequently her cycles had been slightly more regular, but they still varied with intervals from two to five weeks. She also suffered from moderate acne, worse premenstrually. She had had eczema since infancy, with allergy tests and injections between ages five and nine years. A "cortisone" ointment had been beneficial.

Physical examination revealed a well-developed and nourished young woman with moderately severe hirsutism of the face, neck, periareolar and subumbilical areas, sternum, and extremities. There was moderate acne of the shoulders and back, mild of the face. The thyroid was not enlarged. Mild chronic cystic mastitis was present. The remainder of her examination was within normal limits. Urinary 17-KS were 10.2 mg/24 hours.

On Cortef, 5 mg four times daily, her complexion cleared completely, and hair growth on the face diminished impressively. Plasma testosterone remained elevated, however, measuring 202 ng/dl with an upper limit of normal of 80 ng/dl for a female. The dosage of cortisol was therefore increased to 7.5 mg four times daily, and plasma testosterone decreased to 44 ng/dl. On this therapy, not only did the complexion remain clear and hair growth diminish, especially on her face, but menstrual cycles also became regular, and her basal temperature chart showed evidence of ovulation about the fourteenth day of twenty-eight to thirty day cycles. Clotting and severe cramps with her menses disappeared, cystic mastitis cleared, and her eczema remained in remission. After two years, the dosage of cortisol was reduced

to 5 mg four times daily. Plasma testosterone remained within normal range and clinical improvement persisted, so this dosage has been continued for an additional three years.

This young woman, who had been referred primarily for hirsutism, experienced marked improvement not only in this problem but also in acne, chronic cystic mastitis, irregular menses, dysmenorrhea, and eczema, suggesting that all of these disorders had some common factor in their etiology and that this had been corrected by physiologic dosages of cortisol.

ACNE

Acne can be caused by excessive production of androgen in men and women, but it may result from other factors such as ingestion of iodide or chocolate, or skin irritation by certain oils encountered in industry or in cosmetics and hair sprays. If the latter are ruled out, the administration of small physiologic doses of cortisol may produce dramatic improvement. In women, the combination of small doses of cortisol and small doses of estrogen may be necessary for patients who have excess androgen from both adrenals and ovaries, and occasionally patients are encountered whose acne results from excess androgen from the ovaries only and who will improve with estrogen therapy alone. The latter usually have associated ovarian dysfunction and slightly high FSH levels. Those whose acne results from adrenal dysfunction may or may not have associated ovarian dysfunction; this apparently depends upon whether the adrenal dysfunction includes an excessive production of estrogen by the adrenals.

A characteristic of acne due to adrenal androgen is accentuation with or after stress and before and during menses. The former is undoubtedly due to the increased adrenocortical stimulation that occurs with stress. The latter probably also results from increased adrenocortical stimulation associated with the production of adrenal estrogen at this time of the menstrual cycle.

An elevation of urinary 17-KS or of plasma testosterone or DHEA sulfate levels is found in patients with acne due to adrenal or ovarian dysfunction, and the latter is usually associated with slight elevation of plasma FSH. The former may or may not be associated with slight elevation of plasma ACTH. Improvement in acne is manifest much sooner than in hirsutism and should be evident within a month when therapy is effective. An exception is cystic acne such as that described in Case 3

following, where an autoimmune factor may be involved and improvement is slower.

The beneficial effect of small doses of glucocorticoids in acne is so impressive and so safe that it warrants much wider use. Dermatologists have naturally been hesitant to use larger dosages of glucocorticoids that might produce harmful side effects in such a benign clinical condition, but the administration of 5 mg of cortisol four times daily is not only more physiologic but also as safe as, or safer than, the use of broad spectrum antibiotics that is popular in the treatment of acne today. Even the more severe cystic forms of acne may respond dramatically to this type of physiologic therapy, but improvement in cystic acne tends to be much slower, sometimes requiring several months before becoming apparent. Beneficial results in acne are not confined to females, for males with this skin disorder seem to respond equally well.

Case 3 is an example of severe cystic acne that cleared while the patient was receiving low dosage glucocorticoid therapy.

Case 3

This young woman was referred at the age of twenty-seven because of cystic acne that had started six months previously in the sixth month of her first pregnancy. The menarche had occurred at age twelve, and cycles had been regular with intervals of twenty-eight to thirty days, menses lasting five to six days. She had been married for three years and had used an oral contraceptive for two years, conceiving six months after discontinuing it. Her pregnancy was uneventful until the sixth month, when she developed progressive severe cystic acne. This persisted after a full-term, normal delivery. After having no resumption of spontaneous menses by eight weeks postpartum, she was given medication that caused withdrawal flow. In addition, tetracycline, three times daily for two months, had been given for the acne without benefit. She was then advised to resume the oral contraceptive, and three weeks after resuming this, when there was still no evidence of improvement of the acne, she was referred to me. Her health had otherwise been good. She had been adopted in infancy, and her family history was not known.

Physical examination revealed severe cystic acne of the face, neck, chest, and back, rather poor breast development, and a functional systolic murmur over the precordium. The clitoris was not enlarged, and there was no hirsutism. Urinary 17-KS were 6.1 mg/24 hours, and plasma testosterone was less than 30 ng/dl.

Although there was no laboratory evidence of hormonal abnormality, the onset of acne during her pregnancy suggested the possibility of a hormonal relationship; the beneficial effects of physiologic dosages of cortisol in other types of acne, as well as their safety, resulted in a decision to try this type of therapy. Cortef, 5 mg four

times daily, was therefore prescribed. Over the next six months, there was gradual but progressive improvement. The addition of Premarin, 0.3 mg twice daily except during menses for six months, did not produce significant additional benefit, so it was discontinued. An increase in cortisol to 7.5 mg four times daily seemed to cause further improvement, so this was continued. Her acne cleared completely, and regular, ovulatory menstrual cycles resumed.

The preceding patient therefore had a clearing of severe cystic acne on physiologic doses of cortisol, even though hormone studies gave no evidence of abnormality prior to therapy. The development of acne during her pregnancy, with slower response to glucocorticoid therapy, suggests a different cause from the more common type of acne. Perhaps her cystic acne may have been related to an autoimmune factor.

An example of a male with cystic acne who improved on low dosage glucocorticoid therapy at the same time he was being treated for infertility is presented in Case 4.

Case 4

This young man was seen in consultation at the age of twenty-four years because of infertility and low semen volume with low motility (volume 0.5 ml, 60.06 million/ml, 40% motile). He had had cystic acne of his face and chest for approximately eight years, had been married for three years, and tried unsuccessfully for a pregnancy for the previous year. Urinary 17-KS were 16.3 mg/24 hours, and plasma estrogen was 128 pg/ml with the upper limit of normal for a male 70 pg/ml. Plasma cortisol at 9 AM was 16.2 mcg%; thirty minutes after an I.M. injection of 25 units of Cortrosyn this rose to 35.0 mcg%. On Cortef, 5 mg four times daily, sperm count increased to 105 million per cc, but volume remained low. His cystic acne cleared completely, but his wife did not conceive until he had a varicocele corrected by surgery. Subsequently, his wife had a normal baby.

The relatively rapid clearing of this man's acne was a fringe benefit of his cortisol treatment for oligospermia and elevated plasma estrogen, and the safety and effectiveness of this therapy resulted in the patient continuing it after his fertility problem had been corrected.

CHRONIC CYSTIC MASTITIS

The presence of diffuse induration of the glandular tissue of the breasts, sometimes accompanied by cystic nodules, may occur with irregular menses or with apparently normal cycles. The condition is usually most pronounced premenstrually, and it has been attributed to

a relative deficiency of progesterone relative to estrogen, since some cases may be helped by the administration of small doses of progesterone during the luteal phase. When low dosage glucocorticoid therapy has been administered for ovarian dysfunction, associated cystic mastitis has diminished or cleared in practically every case. We have, therefore, tried this therapy in patients with cystic mastitis without apparent ovarian dysfunction, and it has been equally effective. Presumably the mild disorder of steroid metabolism that is responsible for this condition is benefited by small doses of glucocorticoid.

DYSMENORRHEA

It has been estimated that 30 to 50 percent of women of childbearing age suffer from excessively painful menstrual cramps, often associated with nausea, vomiting, diarrhea, headache, fatigue, and nervousness. It has been demonstrated that most of these women have an excessive concentration of prostaglandins E and F_{2a} in their menstrual fluid, often two to three times higher on the first day or two of menstruation than in women who have no dysmenorrhea, and administration of prostaglandin inhibitors, such as ibuprofen, indomethacin, mefenamic acid, and naproxen-sodium, often provides symptomatic relief.[6] Women with ovarian dysfunction often have dysmenorrhea, and when their ovarian dysfunction has benefited from subreplacement dosages of cortisone acetate or cortisol, dysmenorrhea has also disappeared. Hence, such therapy might be helpful in patients with dysmenorrhea with regular menses. It would also be interesting to determine the effect of small doses of glucocorticoids upon prostaglandin content of the menstrual fluid.

Because adrenal estrogen seems to be necessary to avoid hot flashes during normal menses when the ovarian production of estrogen drops, the occurrence of hot flashes during menses can be a symptom of mild adrenocortical deficiency. Hence, tests of adrenocortical function and therapeutic trials of administration of small, physiologic dosages of cortisol may be helpful in patients complaining of hot flashes during menses.

PREMENSTRUAL SYNDROME (PMS)

Another common problem for many women is the occurrence of unpleasant and sometimes debilitating symptoms before the onset of

menses.[7,8] Some of these women have also had chronic allergies or other disorders for which safe, physiologic dosages of cortisol have been prescribed, and several of these patients have reported that their premenstrual symptoms have improved or cleared while they took the cortisol, so this might be a therapeutic option in patients with this disorder.

HYPOTHYROIDISM WITH HIGH CIRCULATING T_3

In 1967, Refetoff, DeWind, and DeGroot[9] reported a familial syndrome that included some symptoms and signs of hypothyroidism associated with an elevated level of serum protein-bound iodine (PBI). Subsequent studies revealed that the high PBI was due to elevated levels of circulating thyroxine (T_4) and triiodothyronine (T_3)[10] that could result from a defect at the level of nuclear receptors.[11] Other reports of patients with apparent partial peripheral resistance to thyroid hormone have appeared subsequently,[12–17] with considerable variability in clinical features.

In 1950, Hill, Reiss, Forsham, and Thorn,[18] in their studies of the effects of ACTH or cortisone in patients with thyroid disorders, reported that administration of either ACTH or cortisone acetate appeared to be capable of increasing basal metabolic rate without changing the level of serum protein-bound iodine of patients taking a constant dose of thyroid. In this same year, Beierwaltes and his associates[19] reported that cortisone seemed to have a calorigenic effect in two patients with untreated myxedema. The following year, Werner and his associates[20] reported evidence that cortisone administration to a patient with myxedema resulted in an increase in BMR, serum protein-bound iodine, and I^{131} uptake and a decrease in serum cholesterol. In 1952, Lerman, Harington, and Means,[21] in a report of physiologic activity of some analogues of thyroxine, described a patient with myxedema who responded poorly to intravenous thyroxine until "cortisone in a dosage of 50 mg twice a day was added." Then "metabolism rose speedily to normal values." The authors then commented that "this type of response . . . may have an important bearing on the fundamental mechanism of the action of thyroid hormone on the cell." Commenting on these studies in 1953, Thorn and his associates[22] stated, "The interesting possibility arises that cortisone aids in the peripheral utilization of thyroid hormone."

In 1977, a patient was seen in consultation who had some symptoms of hypothyroidism associated with an elevated level of circulating T_3, and her symptoms and laboratory findings were restored to normal by cortisone acetate in a dosage of 5 mg four times daily.

Case 5

A fifty-five-year-old female was referred in 1977 because of chronic fatigue for six years. She had an operation for a strangulated hernia at age forty and subsequently began to tire easily. Six years prior to referral, fatigue became worse and she saw a physician who made a diagnosis of possible collagen disorder. Latex fixation and lupus erythematosus tests had been negative. A five-hour glucose tolerance test had been normal except for a slightly low blood sugar level (68 mg%) at the third hour. A neurologist had been consulted, and a diagnosis of Raynaud's phenomenon and possible chronic depression was made. Skull x-rays and an electroencephalogram were normal. She had been given amitriptyline HCL (Elavil®) briefly without benefit. She drank up to ten cups of coffee daily in an attempt to obtain energy, but fatigue persisted, so she was referred for endocrine evaluation. She had four children, had experienced an apparently normal menopause at age forty-nine, about the time symptoms of fatigue increased, and she had received no estrogen therapy. She was sensitive to cold; her hair tended to be dry, but bowels had been regular. A sister had a goiter, but family history was otherwise negative for endocrine disorder.

Physical examination revealed a moderately overweight female with a height of 61¼ inches, weight 156 pounds, blood pressure 124/70, pulse 96 and regular. Her skin was quite dry, and her voice was low-pitched and slightly hoarse. The thyroid gland was not palpable. Reflexes were equal and within normal limits. The remainder of her examination was within normal limits. Hemoglobin was 13.8 gm, WBC 7,840, with 63% neutrophils, 28% lymphocytes, 6% monocytes, 1% eosinophils, and 2% basophils. T_3 sponge uptake was 29%, T_4 was 9.2 µg/dl, and T_3 by RIA was 250 ng/dl. Plasma cortisol at 3 PM was 23.5 µg/dl; thirty minutes after 25 units of Cortrosyn I.M. this rose to 40.5 µg/dl. Total proteins were 6.7 gm/dl, with 4.5 gm albumin and 2.2 gm globulin.

She was told to stop drinking coffee. This improved her ability to sleep; her resting pulse rate decreased to 76 per minute, but chronic fatigue persisted. Because of the evidence for impairment of utilization of T_3, plus the observation that a number of patients given small dosages of cortisone acetate or cortisol for other problems had experienced an improvement in energy on this medication, a trial with this treatment was suggested. After discussion, she agreed to such a trial, so cortisone acetate, 5 mg by mouth four times daily, was started.

When she returned two months later, she reported that she had begun to feel dramatically better about two days after starting the medication, that her energy was now fine, that she no longer had insomnia but fell asleep as soon as her head hit the pillow, and she had resumed playing golf twice weekly. Improvement was so impressive that she went to the library and read more about her adrenals and cortisone,

and this made her worried. She tried stopping the cortisone but became chronically fatigued again, so she resumed it and her energy returned. Her husband was so impressed with her improvement that he reminded her to take the medication regularly. While taking the cortisone, her T_3 sponge uptake was 45%, T_4 was 9.8 μg/dl, and T_3 by RIA was 135 ng/dl. Plasma cortisol at 11 AM was 23 μg/dl and after Cortrosyn rose to 39 μg/dl.

The patient subsequently took cortisone for three years and continued to feel well. She tried stopping it again but developed chronic fatigue after about a week, so it was resumed. She stated, "I just cannot believe this medication could make such a tremendous difference in the way I feel, both mentally and physically."

Subsequently, two similar cases with variable symptoms of hypothyroidism and elevated blood levels of T_3 by RIA have been encountered and these have improved with treatment with cortisol, 5 mg four times daily, even though ACTH tests were within the lower range of normal. It therefore appears that small doses of cortisone acetate or cortisol can correct a partial receptor block for T_3, and it would be interesting to determine whether this therapy would benefit the more severe degrees of block that have been reported previously.

Further studies in other patients have demonstrated that treatment with small dosages of cortisone acetate or cortisol is associated with a decrease in circulating T_3 by RIA when initial levels are high normal or elevated, suggesting that these physiologic dosages improve peripheral utilization of thyroid hormone (Fig. 10). In patients whose initial levels of T_3 by RIA were low normal or low, treatment with these dosages was associated with an increase in T_3 by RIA while patients reported improvement in energy, suggesting that they increased conversion of T_4 to T_3, another mechanism by which they might improve peripheral utilization of thyroid hormone. This would contrast with the effect of larger dosages of glucocorticoids, which appear to decrease the conversion of T_4 to T_3.[23]

If these observations can be confirmed, the predictions of Lerman, Harington, and Means[21] and of Thorn and his group[22] will have been fulfilled. At any rate, patients with symptoms of hypothyroidism associated with high circulating T_3 by RIA and those with evidence of a block in conversion of T_4 to T_3 warrant therapeutic trials with small dosages of cortisol. Patients with a number of acute and chronic nonthyroidal illnesses as well as those with starvation have often been found to have low serum T_3 and normal serum T_4 levels,[24] suggesting either an increased utilization of T_3 or a physiologic decrease in conversion of T_4 to T_3, so

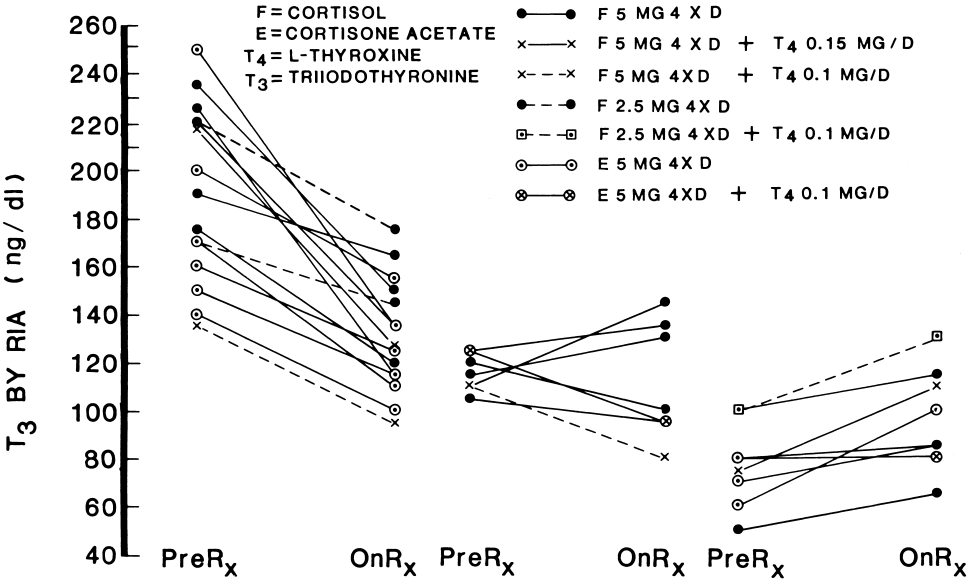

Figure 10. Effects of physiologic dosages of cortisone acetate (E) or cortisol (F) on circulating T_3. Left—subjects whose baseline T_3 was 130 ng/dl or higher; center—subjects whose baseline T_3 was 105–125; right—subjects whose baseline T_3 was 100 or less.

these must be differentiated from those with a pathologic decrease in conversion of T_4 to T_3.

FUNCTIONAL HYPOGLYCEMIA

In recent years, the lay press has emphasized the importance of functional hypoglycemia as a cause of unexplained symptoms, especially chronic fatigue, in many persons. The occurrence of an abnormally low blood sugar after a test dose of glucose implies either an abnormally large production of insulin in response to the glucose or a decreased ability of the body to protect against hypoglycemia. Because cortisol appears to be the body's chief defense against abnormally low blood sugar levels, we have routinely run ACTH tests on patients who are referred with a diagnosis of functional hypoglycemia. In almost every case we have encountered to date, low adrenal reserve has been demonstrated. It is not surprising that functional hypoglycemia should be a manifestation of low adrenal reserve, but this has not been emphasized in the medical literature. In such cases, the administration of small physiologic dosages

of cortisone acetate or cortisol has produced impressive, and sometimes dramatic, improvement. Two case summaries exemplify the value of this type of therapy.

Case 6

This fifty-two-year-old male was referred because of hypoglycemia. His first symptom had been a transient dizzy spell while at lunch with business associates. He had drunk several cups of coffee that morning, so he stopped drinking coffee, but occasional spells of increased nervousness, palpitations, and weakness continued especially in the morning or evening. A five-hour glucose tolerance test at another clinic had shown relatively low blood sugars at the third, fourth, and fifth hours. Valium had been prescribed as symptomatic therapy. He had been under considerable tension during the previous year and had experienced more fatigue. Vitiligo had been present, gradually progressive over the previous five years. His father had senile diabetes and hypertension, and one sister had a diagnosis of low blood sugar and allergies.

Physical examination revealed a height of 72¼ inches, weight 189½ pounds, blood pressure 140/95, pulse 60 and regular. There was moderate vitiligo of the hands, arms, and chest. The thyroid was not palpable, and there was no lymphadenopathy. The liver edge was palpable one finger-breadth below the right costal margin, not tender. The remainder of his examination was within normal limits. An SMA-12 was normal. T_3 sponge uptake was 58%, and T_4 was 6.6 mcg%. Plasma cortisol at 8 AM was 18.3, and post-ACTH this rose to 27.0 µg%.

Because of the evidence of low adrenal reserve with functional hypoglycemia, he was given a prescription for cortisol, 5 mg four times daily. On this medication impressive improvement occurred; energy returned to normal, and symptoms of hypoglycemia did not recur. An ACTH test a year later revealed a plasma cortisol at 10:45 AM of 14.1 µg%; 30 minutes after Cortrosyn this rose to 21.4 µg%. Cortef was therefore continued. Two years subsequently, a repeat ACTH test showed baseline plasma cortisol of 14 at 10 AM; thirty minutes after ACTH this rose to 22 µg%. He has continued to take cortisol, 5 mg three times daily, and has continued to feel well.

At the time of his last visit, three and one-half years after beginning therapy, weight was 194¼ pounds with shoes, blood pressure 114/70, pulse 80 with occasional premature beats. He had stopped drinking caffeine-containing beverages, but he continued to smoke up to one pack of cigarettes daily. The liver edge was still palpable one finger-breadth below the right costal margin. An SMAC was normal, including normal cholesterol, triglycerides, alkaline phosphatase, bilirubin, LDH and SGOT.

The fact that this 55-year-old business man continued to take cortisol tablets three or four times daily for three years reflects how functional hypoglycemia can be a significant problem and also how taking a

medication four times daily can be achieved if it is being effective. It would be interesting to know whether his nicotine addiction was contributing to the hypoglycemia.

Case 7

The patient was referred at the age of twenty-three years because of functional hypoglycemia. He had been having intermittent symptoms of weakness, palpitation, and anxiety for nine months with onset shortly after an attack of "intestinal flu." He had been referred to a neurologist a month previously, but neurologic examination and electroencephalogram were within normal limits. His general health had been good, and he had had no serious illnesses or operations. A five-hour glucose tolerance test had shown hypoglycemia at three hours.

Physical examination was within normal limits except for mild acne and a positive Chvostek's sign. Height was 70¼ inches, weight 169½ pounds, blood pressure 100/70, pulse 120 and regular. An SMAC was normal. Plasma cortisol at 8:30 AM was 18.5 µg%; thirty minutes after Cortrosyn this rose to 27.4 µg%.

A diagnosis of low adrenal reserve and probable functional hypoglycemia was made, and he was given cortisone acetate, 5 mg four times daily. On this program his symptoms of weakness and palpitation cleared and energy returned impressively. He also experienced improvement in acne, for which he had been treated by a dermatologist with variable results. A repeat ACTH test later showed a plasma cortisol at 12 noon of 11.5 mcg%; thirty minutes after Cortrosyn this rose to 20 mcg%. He has continued to take Cortef, 5 mg four times daily, chiefly because of its benefit to his complexion, and he has continued to feel well.

This young man's symptoms were similar to those of patients with the chronic fatigue syndrome (see below) except that they were intermittent and apparently related to functional hypoglycemia.

UNEXPLAINED CHRONIC FATIGUE ("THE CHRONIC FATIGUE SYNDROME")

Every practicing physician has encountered a number of patients complaining of unexplained chronic fatigue. When a routine history and physical examination plus urinalysis, blood counts, and screening blood chemistries fail to reveal any abnormalities, many of these patients have been referred to psychiatrists, who usually find no significant psychiatric disorder. These patients differ from neurotics in that they seem to be anxious to be active and work, but they feel too tired to undertake or accomplish the things they would like to do. Conditions that should be

ruled out include mild hypothyroidism, low-grade chronic infection of a tooth, of the sinuses, or of the urinary tract that has been otherwise asymptomatic, or obscure malignancy.

If none of these conditions are found, an ACTH test should be performed, as many of these patients will be found to have low adrenal reserve or a low baseline plasma cortisol level, suggesting inadequate stimulation of the adrenal by the pituitary. These findings are characteristic of the postviral syndrome, as discussed in Chapter 9, but they also may occur in chronic allergies as discussed in Chapter 7. In such cases, impressive symptomatic improvement will occur with administration of 5 mg cortisol four times daily. Most allergies, in addition to causing fatigue, have characteristic manifestations of urticaria, dermatitis, rhinitis, asthma, gastrointestinal disorders, or headaches, but sometimes fatigue seems to be the only symptom.

Occasionally a patient is encountered complaining of chronic fatigue whose ACTH test is normal, and no other evidence of abnormality can be found. Psychoneurosis or depression seems unlikely because characteristic symptoms are absent and patients with depression usually have an excessive adrenal response to ACTH stimulation,[25,26] yet a therapeutic trial with small doses of cortisone acetate or cortisol may produce symptomatic benefit. This effect came as a surprise, and I was inclined to attribute it to the presence of an undetected mild allergy until recently when it was noted that the administration of these dosages of cortisone acetate or cortisol can result in a decrease in circulating T_3 by RIA. Early in this chapter a patient was described with symptoms of hypothyroidism and a high T_3 by RIA, suggesting a partial receptor block for triiodothyronine that was corrected by cortisone acetate, 5 mg four times daily. It was also noted that when patients with baseline T_3 by RIA levels in the high normal range were given small dosages of cortisone acetate or cortisol for any reason, such as irregular menses or hirsutism, the T_3 by RIA level decreased at the time the patient reported an improvement in energy. The possibility must therefore be considered that at least part of the clinical improvement associated with administration of small doses of these steroids may result from an increased uptake of triiodothyronine by the cells. This observation also suggests that a basic mechanism of action of physiologic dosages of glucocorticoids may be an increased cellular uptake of triiodothyronine. This possibility, as well as the possibility that utilization of other hormones or

metabolic substances might be enhanced in this fashion, should be investigated further, since this might be a mechanism of the "permissive effect" of glucocorticoids suggested by Ingle[27] or of their effect as biological amplifiers.[28]

These observations and impressions, which were discussed in the first edition of this book that was published in 1981, still apply because no attempts have apparently been made to confirm them, but meanwhile unexplained chronic fatigue has achieved a large amount of publicity as the "chronic fatigue syndrome." Although there has been difficulty in reaching a consensus regarding its definition,[29,30] it is obviously a relatively common diagnostic and therapeutic problem for practicing physicians. In 1991, Demitrack et al. published an interesting study[31] that concluded that activation of the hypothalamic-pituitary-adrenal axis was impaired in cases of this disorder, but they made no suggestions regarding possible therapy.

In the same year that the first edition of this book was published (1981), Poteliakoff[32] reported that patients with either acute or chronic fatigue had evidence of adrenocortical deficiency by lower plasma cortisol levels as well as higher blood eosinophil counts than normal controls, but this report apparently also received little attention. The reputation of glucocorticoid therapy had apparently become so bad that no one wanted to hear or read any more about it!

When it became apparent that the well documented requirement for normal physiologic amounts of cortisol for the development and maintenance of normal immunity had been overlooked or forgotten, a review of the impressive amount of evidence for this important relationship was published,[33] but it also received relatively little attention. A subsequent report discussing the causes for this unique situation in clinical medicine, where a promising therapeutic approach was being overlooked or ignored, and reviewing the remarkable potential of safe, physiologic dosages of cortisol, was also published,[34] and a growing group of primary care physicians, mostly allergists and general practitioners, became aware of the effectiveness and safety of this therapy. In the last few years, reports of evidence that patients with rheumatoid arthritis and other autoimmune disorders have defects in their HPA responses that become evident only under certain circumstances and that result in their having potential deficiency in cortisol production in response to stress provide further stimuli for study of these relationships. It has become evident

that mild adrenocortical deficiency can result not only from a deficient production of cortisol by the adrenals (primary adrenocortical deficiency or low adrenal reserve), or from a deficient production of ACTH by the pituitary (secondary adrenocortical deficiency), or by a deficient production of CRF by the hypothalamus (tertiary adrenocortical deficiency), but also by a defect in cellular receptor function for cortisol. This is a condition in which the HPA axis produces an adequate amount of cortisol, but a defect in the cellular receptors for this hormone prevents an adequate amount reaching the interior of the cell where it must produce its effects. It is therefore characterized by symptoms of adrenal deficiency in spite of adequate or even excessive amounts of cortisol in the blood.[35] Under these circumstances, plasma ACTH might be low, normal, or elevated, depending upon the response of the HPA axis to the normal or elevated cortisol levels in the blood, and symptoms can vary from chronic fatigue to various manifestations of adrenogenital syndromes.

These observations indicate that determinations of plasma levels of cortisol and ACTH do not always determine whether a patient's symptoms are due to adrenal deficiency, *so therapeutic trials with small, physiologic dosages of cortisol are advisable in patients with characteristic symptoms of adrenocortical deficiency, including those with the chronic fatigue syndrome, regardless of the results of laboratory tests.* Tests are helpful in determining the nature of the problem and whether other additional medication, such as thyroid or an antibiotic, is indicated. Hence, all patients with unexplained chronic fatigue should have tests of adrenocortical function and therapeutic trials with safe physiologic dosages of cortisol.

TRAVEL FATIGUE (JET LAG)

In Chapter 3, it was noted that a diurnal variation in plasma cortisol levels occurs normally, with a peak shortly after arising following a good night's sleep and a low point shortly after retiring at night. When a person travels to different time zones, especially when differences of several hours occur, adjustment of the hypothalamic-pituitary-adrenal axis to the new sleep-wake schedule may require five to ten days. Meanwhile, the person tends to feel chronically fatigued. Because patients on low dosage glucocorticoid therapy do not seem to experience this "jet lag," presumably because their therapeutic program tends to decrease diurnal variation and because they adjust their dosage schedule to the

new time schedule immediately, a short course of 5 mg cortisol four times daily for a week may be an effective yet safe method of avoiding or treating this disorder.

POLYMYALGIA RHEUMATICA

This is a condition with many symptoms similar to those of patients with rheumatoid arthritis, but it occurs almost exclusively in persons over the age of 50, and the average age of onset is 70. Between 10% and 20% of patients with this disorder have associated cranial arteritis (also known as temporal or giant cell arteritis) with persistent and debilitating headaches as well as muscular aches (myalgia) and malaise. Laboratory studies typically show a markedly elevated erythrocyte sedimentation rate and treatment with prednisone has been recommended, although tests of adrenocortical function have not been mentioned. I have not had occasion to study or treat any patients with this disorder, but tests of adrenocortical function and therapy with physiologic dosages of cortisol as in patients with rheumatoid arthritis should be considered. Initial dosages may need to be higher, but tapering to physiologic maintenance dosages might be safer, and probably as effective as the prednisone treatment that is generally recommended.

FIBROMYALGIA

This is another condition that is being more frequently recognized in recent years, but with which I have had no personal experience. It is characterized by generalized achiness, pain and stiffness, chronic fatigue, and disturbed sleep, but no evidence of infection or inflammation on laboratory tests. It occurs primarily in women, with onset between age 20 and 60, but it also may occur in older women, and its treatment has been essentially supportive. Because its symptoms are similar to those of adrenal deficiency, tests of adrenocortical function would be interesting, and therapeutic trials with safe, physiologic dosages of cortisol might be helpful.

LEUKEMIA AND LYMPHOMA

The reports that glucocorticoid therapy produces lysis of lymphoid tissue resulted in therapeutic trials with pharmacological dosages in

patients with lymphoid leukemia and lymphoma. Although transient beneficial effects were observed in patients with both acute and chronic lymphoid leukemia and in patients with lymphoma, there was no apparent effect on the ultimate outcome of these diseases. Relatively short courses of pharmacologic dosages of glucocorticoids are still being used in conjunction with combined therapy with chemotherapeutic and cytotoxic agents in these disorders. In view of the safety of prolonged uses of physiologic dosages and because they seem to enhance immunity, a property that seems to be important to resistance to malignancy as well as to infections, the prolonged administration of physiologic dosages of cortisone or cortisol, alone or in conjunction with chemotherapeutic or cytotoxic agents in such disorders might be helpful.

CARCINOMA OF THE BREAST OR THE PROSTATE

Two other types of malignancy in which therapy directed towards the adrenal gland has shown evidence of at least temporary benefit have been carcinomas of the breast and of the prostate gland. Since normal breast development depends upon adequate estrogen stimulation, it was not surprising to find that many cases of cancer of the breast seem to be partly dependent upon estrogen stimulation. In such cases, removal of the ovaries, the major source of estrogen in premenopausal women, has produced impressive benefit, although this has been only temporary. After cortisone acetate or cortisol became available, it became surgically feasible to remove the adrenal glands, the other glandular source of estrogen, and in such patients further clinical remissions, sometimes of several years duration, occurred. Ultimately, the cancer would begin to grow again, however, so such procedures were still of only temporary benefit.

Because total adrenalectomy is a major surgical procedure that is not available in all hospitals, attempts were made to suppress the adrenal production of estrogen by the administration of suitable dosages of glucocorticoids, and in such cases, temporary remissions have also been observed. A suppressive dosage of 10 mg four times daily of cortisol in the unstressed state will inhibit the adrenal production of estrogen. This also tends to make the patients' adrenals sluggish so that they will not react to stress in an adequate fashion, so such patients must be given additional steroid at times of stress as though they were adrenally in-

sufficient. As long as the basic dosage of cortisol does not exceed 10 mg four times daily, they will not develop evidence of hypercortisolism, however. Physiologic dosages of androgen will help to protect against the easy bruisability and ecchymoses that accompany deficiency of adrenal androgen.

With more recent evidence that the presence of estrogen receptors in malignant tissue may determine the effectiveness of ablative therapy directed towards the ovaries or adrenals or both, there has been emphasis on using such testing to avoid unnecessary major surgical procedures such as adrenalectomy. Unfortunately, the presence of estrogen receptors is not as specific for predicting favorable responses to ablative or hormone therapy as was initially hoped, 40–45 percent of patients with such receptors failing to improve, and 8 percent without such receptors improving after oophorectomy or adrenalectomy.[36]

With the use of suitable suppressive dosages of glucocorticoid, provided patients take them on an optimum schedule, it is possible that the beneficial effects of adrenalectomy in metastatic breast cancer might be obtained without submitting the patient to the major surgical procedure. This, of course, would not apply to ovariectomy, but this is a less strenuous surgical procedure. Furthermore, until our knowledge of the cause and treatment of cancer of the breast is more complete, the relative safety, plus the logic, of glucocorticoid therapy of this type would warrant its being tried in patients regardless of whether estrogen receptors were present in the tumor tissue.

The recent use of cytotoxic agents in the treatment of metastatic breast cancer has often included short courses of pharmacologic dosages of glucocorticoids, but it is possible that persistent administration of physiologic dosages of cortisol might further improve the results of this type of therapy by persistently suppressing adrenal estrogen production as well as protecting against adrenocortical deficiency.

Recently, Santen and his associates have reported that aminoglutethimide, a chemical that blocks estrogen synthesis from androstenedione, lowers circulating and urinary levels of estrogen as well as adrenalectomy,[37] and they suggest that it may have value in the treatment of breast cancer. Because it also blocks conversion of cholesterol to pregnenolone, it inhibits cortisol production, and patients have to be given replacement cortisol during its administration. This raises a question whether antitumor effects of aminoglutethimide would be greater

than those of replacement dosages of cortisol alone, provided such replacement dosages are administered on an optimum schedule for producing adrenal suppression. Replacement dosages of cortisol should be less toxic.

It is also possible that physiologic dosages of cortisone or cortisol might help patients with any type of malignancy by improving their resistance to cancer. At present, two therapeutic principles seem important in the treatment of malignancy: the first is to destroy the malignant tissue, and cytotoxic drugs have produced impressive advances in this area. The second is to improve the resistance of the host. This principle has received less attention but may be equally important in the ultimate success of the therapy by impairing recurrences of tumor growth. Benjamini and Rennick[38] summarized the status of cancer immunotherapy, but glucocorticoids were not mentioned.

Treatment of patients with metastatic carcinoma of the prostate gland, where the tumor may be dependent upon androgen stimulation, has similar therapeutic possibilities. Historically, this was the first type of metastatic cancer that was reported to respond beneficially to adrenalectomy in patients who had had previous orchidectomy.

POSTOPERATIVE STATES

Another possible use of physiologic dosages of glucocorticoid is in certain postoperative states. When patients with adrenal insufficiency come to surgery, they are routinely given 100 mg of hydrocortisone sodium succinate (Solu-Cortef) intramuscularly one hour before surgery is begun; depending upon the illness of the patient and the extent of the surgical procedure, postoperatively they may receive 100 mg I.M. every eight hours for the first twenty-four hours, gradually tapering over the next week to their maintenance dose, or lower amounts down to 50 mg eight hours after the surgery followed by a resumption of usual maintenance dosage by mouth. Such patients have remarkably smooth postoperative courses, requiring little morphine or other pain-relieving medications, with restoration of strength, ambulation, and a good dietary intake sooner than many patients with normal adrenal function undergoing similar surgical procedures.

Beneficial effects of cortisone acetate in the postoperative state were reported very shortly after this steroid became available for clinical

use,[39] but after harmful side effects with large doses were reported, possible beneficial effects of this type were apparently forgotten. Concerns regarding steroid administration in postoperative states, of course, are the possibility of interference with wound healing, increased susceptibility to infection, or possible masking of postoperative complications. During the past forty-four years, we have had sufficient experience with patients with adrenal insufficiency undergoing surgical procedures to indicate that dosages of cortisol in the physiological range that has been recommended will not cause any harmful effects. Wounds heal normally, and there is no indication of increased bacterial infection. None of these patients suffered complications of surgery, but experience with other patients who had previously been taking glucocorticoids and hence were given supplementary Solu-Cortef at the time of surgery indicates that such dosages do not mask surgical complications. Further studies of the potential value of this type of therapy in postoperative patients therefore seem warranted, provided care is taken to avoid excessive supplementary dosages or continuation of supplementary dosages too long, either of which may produce toxic effects such as hypokalemia.

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Chapter 11

SUMMARY, SPECULATION AND CONCLUSIONS

These observations, spanning over fifty-two years of experience with glucocorticoid therapy, finally culminating with the evidence that the influenza virus attacks the human body by impairing the production of adrenocorticotropic hormone (ACTH) by the pituitary gland, thereby impairing the production of cortisol, the only hormone that is absolutely essential for life, provide a fitting culmination for this third edition of *Safe Uses of Cortisol*. At the age of 88 years and legally blind with macular degeneration, my days of active investigation and research related to the cortisol story are drawing to a close. However, with the help of my magnifying glasses and computer, plus the help of my daughter Leslie, who continues to review my manuscript and see that it gets to the publisher in addition to helping in so many other ways, plus the help of my part-time secretary Debbie Smith, who provides invaluable day-to-day help, I hope to continue to suggest ways in which the medical profession and pharmaceutical industry can help to improve the delivery of medical care to patients. Our present patent laws do not always promote the best medical care for the patient, so they should be re-examined in an attempt to improve this situation.

I hope the previous chapters have convinced the reader that cortisol therapy can be safe and that the potential for this type of therapy is sufficiently great to warrant further study. Since this book was first published, few reports have answered any of the questions that were raised then in this chapter, but further experience and reports from other clinics have provided additional reasons for hoping that studies to answer at least some of these questions will be undertaken.

In conclusion, I would like to indulge in further speculation regarding a few of the possibilities raised in the previous chapters. Although some of these suggestions may seem rather remote and tenuous, they may provide a stimulus for future studies.

If the adrenal cortex does produce an anti-sodium-retaining factor as postulated in Chapter 3, it is possible that some cases of hypertension may result from a deficiency of this factor. Such cases would probably have low levels of renin because of the relative excess of sodium-retaining hormone, but the actual levels of sodium-retaining hormone might not be elevated. The possible sequence of events in the development of hypertension in such cases might be as follows: (1) a deficient intake of water relative to salt, producing an increased requirement for anti-sodium-retaining factor; (2) with prolonged maintenance of such a state, the ability to produce anti-sodium-retaining factor might become deficient or exhausted; (3) excessive sodium retention and hypertension would then result. The possibility that a relative deficiency of water intake might contribute to the production of hypertension should therefore be studied, as well as the possibility that an increased intake of water in addition to a decreased intake of sodium might be beneficial in the treatment of hypertension, provided the steroid abnormality or renal damage has not become irreversible.

Mild adrenocortical deficiency, whether due to low adrenal reserve, to decreased stimulation by the pituitary or the hypothalamus, or to a partial receptor block to cortisol, should be further investigated, both with regard to its definition and its relation to conditions such as allergies, autoimmune disorders, the postviral syndrome, and the chronic fatigue syndrome. Why it seems to be temporary in some instances and permanent in others also needs clarification.

Studies of the relationship of adrenocortical hormones to immunity should include not only the processes involved in resistance to infections of all types—viral, fungal, bacterial, rickettsial, and protozoal—but also those involved in resistance to malignancy. Studies are needed to determine factors involved in protection of the body from the development and growth of malignant cells as well as a continuation of studies of methods of destroying malignant cells.

The relationship of adrenocortical response to infection must be related to the response to other stresses. For example, evidence suggests that as an initial response to stress increased utilization of cortisol occurs. This, plus the increased need for cortisol to combat the stress, results in symptoms and changes in blood chemistry consistent with relative adrenal insufficiency during the shock phase of the alarm reaction. The adrenals then apparently respond with increased production of

cortisol as a result of stimulation by ACTH. Because there is increased utilization of cortisol, plasma cortisol levels may not increase or may even decrease, but a drop in circulating eosinophils probably reflects the increased glucocorticoid effect. Such changes occur with bacterial infections, but the lack of leukocytosis, granulocytosis, lymphopenia, or eosinopenia in viral infections suggests an absence of normal adrenocortical response, and our observation of low plasma cortisol levels during the early phase of influenza is consistent with this possibility, but other factors may also contribute to these differences. The adrenal response to stress therefore appears to be an important component of the body's nonspecific mechanism of resistance to infection; in fact, under some circumstances it may even contribute to the initial stimulus that brings the HPA axis into action, and the sufficiency of the HPA response may determine the outcome of the infection. If it is adequate, the host will recover uneventfully or possibly might not develop any clinical symptoms of illness.

If this speculation is correct, the nonspecific symptoms of illness, such as malaise, anorexia, and fatigue, may be manifestations of relative adrenal insufficiency and may not be a necessary component of the body's defense mechanism at all. Consistent with this possibility is the observation that some patients taking cortisone acetate or cortisol, 5 mg four times daily, upon developing symptoms of an incipient upper respiratory infection and doubling their dosage of steroid, experienced a complete clearing of symptoms, suggesting that the infection had been aborted. Others on the same treatment continued to develop symptoms of the illness, suggesting either that they had a more virulent infection or that their basal resistance was lower and, hence, not raised sufficiently to prevent the illness. If the latter is correct, increasing the dosage of steroid by three- or four-fold might be more effective in aborting the illness. Studies of persons who report they never had common respiratory illnesses to determine how their immune response differs from that of people who are subject to such infections would be of interest. Also, studies of differences in adrenocortical function and in the state of the immune mechanism during the spring and autumn, the seasons of greatest incidence of respiratory illnesses in temperate climates, compared with summer and winter might be helpful.

Factors determining whether large dosages of glucocorticoids enhance or impair immunity must be clarified. Both the timing of administration

relative to the onset of infection and the size of the dosage seem important. If cortisol or other glucocorticoids are administered in sufficient dosage to suppress the hypothalamic-pituitary-adrenal response *prior to* exposure to infection or toxin, resistance may be lowered or possible distorted, whereas comparable large doses, perhaps provided they are not too large, administered *after* exposure to infections or toxins may improve resistance. The studies of Thomas and Good,[1] which demonstrated that the Schwartzman phenomenon of hemorrhagic necrosis at the site of injection of toxin occurred when large doses of cortisone were administered prior to, but not when they were administered after, the injection of toxin, are consistent with this clinical impression. Because the Schwartzman phenomenon is apparently a type of autoimmune reaction, these studies also suggest that autoimmune disorders may be related to an impairment of the immune process prior to the onset of a stress such as a severe emotional upset, an infection, or exposure to toxin.

Observations of Kass and Finland made shortly after cortisone was introduced[2] indicate that the *size* of glucocorticoid dosage also may be a determining factor in response to infections. They noted that the amount of cortisone required to restore adrenalectomized mice to approximately the original state of resistance to infection was five to ten times the amount that maintained uninfected adrenalectomized mice in an apparently normal state, whereas approximately twenty to fifty times the minimum maintenance dosage must be given to depress the mouse's resistance below that of an intact animal. In our clinical observations, the ratios are not so great, a mere doubling of the maintenance dosage often apparently being sufficient to protect against common respiratory infections, and an excess of glucocorticoid much less than the twenty- to fifty-fold increase necessary to reduce resistance in the adrenalectomized mouse may be sufficient to impair resistance in the human.

The evidence that factors that are known to lower resistance to infection, such as lack of sleep, poor nutrition, and excessive fatigue, also increase the strain on the adrenal cortex is consistent with the importance of this gland in protecting against disease. That some persons never have common respiratory illnesses suggests that there is a great difference in individual innate resistance, at least to some viral infections. The characteristic lowering of resistance to bacterial infections following viral infections may be related to an inhibition or distortion of the hypothalamic-pituitary-adrenal mechanism by the viral infection or by

depletion of glucocorticoids in response to the infection. Conversely, increased resistance to other stresses that occurs during the stage of resistance of the general adaptation syndrome may be at least partly due to a state of increased adrenocortical activity.

After the initial "shock" response to acute stress or infection, the countershock phase occurs, characterized by evidence of increased production of cortisol, and when this response, plus any specific immune response such as increased production of antibodies, is sufficient, the infection is overcome and the patient recovers. If the subject's resistance is lowered due to chronic debility, poor nutrition, inadequate rest, previous stress, or infection, the immune response, including production of cortisol, may be impaired, and the symptoms and duration of the illness may be greater. In some circumstances, the infection itself, as in certain virus infections, may interfere with normal hypothalamic-pituitary-adrenal response, and the patient may succumb rapidly either to the initial infection or to some complicating infection as a result of interference with normal host defenses. In such cases, the administration of proper additional dosages of cortisol may be beneficial in overcoming the infection more quickly or may even be lifesaving. It is essential that other supportive therapy and, in the presence of bacterial infections, suitable antibiotics be administered concomitantly with the steroid.

When such a program of therapy is initiated, it appears to be advisable to continue it until the patient is completely recovered and feeling well. This certainly applies to antibiotic therapy, which should be continued for several days after the patient has recovered in order to minimize the chance of recurrence. If an antibiotic is continued for a minimum of 10 days, or until a patient has been symptom-free for at least 5 days, recurrence seems to be less likely. The increased dosage of cortisol should be continued until the patient is feeling well, then tapered to the preillness maintenance level within a few days, or in patients who have not previously been receiving glucocorticoid therapy, tapered and withdrawn completely. If the larger dosage of cortisol is continued too long, hypercortisolism with its well-known harmful effects may occur.

Studies of the HPA axis, especially of adrenocortical function, in the initial stages of virus infections, including AIDS and rapidly fatal Ebola virus infections, or during and after unusually severe stresses, should be helpful in determining whether supplementation with cortisol or other adrenocortical hormones such as DHEA might be indicated in order to

decrease chances of development of the infectious illness or of subsequent autoimmune disorders. With the evidence that the latent period in AIDS infection is a time of intense competition between the virus and the immune system,[3] any therapy that will support and enhance the immune system might contribute to a successful outcome of the battle. Hence, physiologic dosages of cortisol might help the immune system in this battle, providing the medical profession can be convinced of the safety and effectiveness of physiologic dosages.

The mechanism by which glucocorticoids increase resistance needs further investigation. Additional studies of the effects of physiologic as well as pharmacologic dosages of glucocorticoids upon immune globulins are needed, and because of the apparent important role of interferon in the immune response[4] plus the similarity of some of its effects to those of physiologic dosages of glucocorticoids, the effect of glucocorticoid upon interferon production and activity should be investigated. Because of proven importance of the complement system in defense against microbial infection, especially the contribution of properdin and the alternative pathway of complement activation to natural, nonimmune defense as well as to amplifying antibody-dependent reactions,[5] the effect of varying dosages of glucocorticoids on this system should be studied.

The factors affecting the resting levels and responses to stress of plasma cortisol and possibly other adrenal cortical steroids such as DHEA need further study. The significance of the diurnal pattern of production of these hormones must be determined. It is known that when subreplacement dosages of cortisone acetate or cortisol are administered, ACTH is secreted in its usual diurnal pattern, but in smaller amounts. This may explain part of the beneficial effect of subreplacement dosages of cortisone or cortisol, but more information is needed regarding factors that affect ACTH stimulation or suppression. Because "ectopic" secretory episodes of cortisol occur most frequently between the sixth and eighth hours of sleep and the fewest episodes two to four hours prior to the onset of sleep, it appears that adequate sleep increases sensitivity of the hypothalamic-pituitary-adrenal mechanism with increased production of ACTH and plasma cortisol, whereas fatigue is associated with a converse effect. Nutrition also probably affects the function of the hypothalamic-pituitary-adrenal axis, and intake and utilization of vitamin C seem especially likely to affect the efficiency of this

axis. Hence, further clarification of the relationship between ascorbic acid metabolism and adrenocortical function is needed.

Studies of the role of leukocytes in the immune response in recent years have provided fascinating insight into the actions of these cells. It is evident that thymus-derived or T-lymphocytes provide the nonspecific, cellular response to infection, and B-lymphocytes provide specific antibodies. The T-lymphocytes can be further divided into helper T-cells, which assist the immune response, including the production of antibody by B-cells, and suppressor T-cells, which regulate and shut off the immune response when it has achieved its purpose. Because a deficiency of suppressor T-cells appears to be responsible for the development of at least some autoimmune disorders, wherein the body develops antibodies to some of its own tissues or immune complexes that interfere with normal functions, and because cortisol counteracts autoimmune disorders, it is possible that cortisol stimulates or regulates suppressor cell activity under at least some circumstances. Excessive suppressor cell activity might be a mechanism by which excessive dosages of glucocorticoids impair resistance. Hence, studies of the effects of physiologic versus pharmacologic levels of cortisol upon T-cell activity should be interesting.

The enthusiasm in recent years for delving into studies of activity at the subcellular level is both understandable and proper, but the importance of continuing studies of the whole organism and the manner in which it regulates the activities at the cellular and subcellular level must not be neglected or overlooked. How these activities or their impairment contribute to the production or prevention of disease must also be determined.

For example, HLA factors appear to be involved in susceptibility to certain types of disease, such as rheumatoid arthritis,[6] but they seem to be merely permissive or contributory factors, not causal factors. The fact that the only substance normally produced by the body that counteracts autoimmunity is cortisol suggests that more studies of the relationship of *physiologic* amounts of cortisol to normal immunity as well as studies of how *inadequate* amounts of cortisol might contribute to the development of autoimmune disorders should be helpful. Inherited or familial factors are probably involved.

The relationship of stress to these and to other disorders such as hypertension or peptic ulcers also suggests that studies of the factors that

determine how an individual responds to stress and how this response contributes to the development of various stress diseases might not only help in their treatment but also in their prevention.

The mechanism of improvement in energy and feeling of well-being that occurs in some persons while taking subreplacement dosages of cortisone or cortisol needs further study. This seems to be different from the euphoria that may occur with pharmacologic dosages of glucocorticoids in that it is not associated with any tendency to psychosis, and it may persist for long periods of time after withdrawal of the glucocorticoid in contrast to the relatively rapid loss of the euphoria after the discontinuance of pharmacologic dosages. The evidence that subreplacement dosages may correct a partial receptor block for triiodothyronine plus the evidence that high normal circulating levels of T_3 by RIA decrease during the administration of subreplacement dosages suggests that an improvement in receptor function for triiodothyronine may be a mechanism underlying the apparent nonspecific improvement in energy that occurs with this dosage. It is also evident that an improvement in energy occurs in patients with allergic disorders when they receive subreplacement dosages, so the effect of this therapy upon cellular receptors for triiodothyronine in patients with the "immediate type" hypersensitivity disorders would be of interest.

It has been demonstrated that the active form of thyroid hormone is T_3 and that T_3 acts within the nuclei of cells. Hence, T_3 must move from the bloodstream, where it is circulating, to the cell nucleus, where it combines with receptors and produces an increase in metabolism. Because T_3 is a protein, it cannot cross cell membranes without help, and this help is provided by cellular receptors. The ultimate action of thyroid hormone therefore depends upon the efficacy of its receptors as well as upon other critical steps in its utilization. Because cortisol appears to improve the utilization of T_3 in patients with symptoms of hypothyroidism and elevated T_3 by RIA, and because it seems to cause a decrease in circulating T_3 by RIA when this is in upper normal range, it seems likely that cortisol, at least under some circumstances, improves the function of the T_3 receptor.

In patients with hypothyroidism, on the other hand, cortisol does not cause a decrease in circulating T_3 by RIA but rather tends to produce an increase. This observation, plus the decrease in circulating T_4 that often occurs simultaneously, and the improvement in energy manifested in

such patients, suggests that the cortisol is enhancing conversion of T_4 to T_3. Thus physiologic dosages of cortisol appear to be capable of improving thyroid hormone activity by increasing conversion of T_4 to T_3 as well as by enhancing T_3 effect on the cell.

In hypothyroidism, an increase in T_3 receptors would be expected, so the failure to produce a decrease in circulating T_3 suggests that the effect of cortisol on receptor function may depend on the number of T_3 receptors. Hence, if the number of T_3 receptors is high, but the amount of T_3 is low, as in hypothyroidism, cortisol has little or no effect; if the number of T_3 receptors and level of circulating T_3 is normal, it improves receptor function. If the number of unoccupied T_3 receptors is low, as in hyperthyroidism, clinical experience suggests that T_3 receptor activity is also increased by cortisol. The patient in Case 8 of Chapter 4, a man with congenital adrenal hyperplasia who had a recurrence of hyperthyroidism after treatment with cortisol, 5 mg four times daily, seems to support this speculation. If this is true, administration of small dosages of glucocorticoid to patients with untreated Graves' disease might cause an increase in hypermetabolism, but administration with antithyroid therapy does not seem to produce this effect. The observation, referred to in Chapter 8, of Hill and his associates[7] that the administration of ACTH or cortisone to patients with Graves' disease seemed to produce a transient exacerbation followed by a decrease in thyroid function suggests that larger dosages may counteract the underlying cause of this disorder and is consistent with the beneficial effect of glucocorticoids in autoimmune diseases.

Finally, although much has been learned regarding the components of energy metabolism and of the immune response, little is known of the mechanisms regulating these vital processes. Circumstantial evidence suggests a significant role of physiologic amounts of cortisol in such regulation, so it is therefore time to discard the indiscriminate fear that has resulted from the harmful side effects of excessive dosages of glucocorticoids and return to the study of the role of physiologic amounts of the natural glucocorticoids in maintaining health and energy, and of the potential of safe, physiologic dosages of these steroids in improving the body's overall resistance to infection, malignancy, and other stresses.

As this third edition of this book is concluded, little needs to be added that has not been covered in the discussions of the exciting new advances discussed in the sections on autoimmune diseases, allergic

disorders and unexplained chronic fatigue ("the chronic fatigue syndrome"). Any patient with unexplained fatigue or a condition with fatigue not explainable on the basis of cardiac, hepatic, pulmonary or renal disorders should have determinations of plasma cortisol and ACTH levels, a Cortrosyn test and possibly a therapeutic trial with cortisol, 5 mg four times daily. This would include stress disorders, the Gulf War Syndrome, and the post-polio syndrome. The evidence that at least some cases of an autoimmune disease such as rheumatoid arthritis may be kept in permanent remission by persistent administration of safe, physiologic dosages of cortisol as discussed in Chapter 6, and that prolonged treatment of severe allergic disorders with such dosages of cortisol can not only restore normal health, but also restore normal growth and development as discussed in Chapter 7, and that chronic autoimmune thyroiditis may subside at least temporarily, and possibly permanently, after suitable physiologic dosages of cortisol as discussed in Chapter 8, will hopefully encourage further use of this therapeutic approach by primary care physicians as well as by rheumatologists and allergists, provided they bear in mind and observe the precautions regarding the proper use of physiologic dosages discussed in Chapter 4.

Evidence that the influenza virus attacks the human body by impairing the production of ACTH raises the question of whether diseases caused by the Ebola virus, the West Nile virus or SARS have similar etiologies. If they do, their treatment with physiologic dosages of cortisol might be helpful or even life-saving.

A type of treatment that has achieved as bad a reputation as that of the use of glucocorticoids cannot expect a dramatic change overnight. Because of the unique situation with regard to cortisol therapy, usual promotional programs by pharmaceutical companies will probably not occur for this type of therapy, so hopefully letters to the editors of medical journals by practicing physicians reporting favorable results in patients will convince them that this therapeutic approach is both valid and safe.

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APPENDIX

NORMAL VALUES FOR TESTS LISTED IN CASE SUMMARIES

Urine	
17-ketosteroids	5–15 mg/24 hr
17-hydroxycorticosteroids (Porter-Silber)	5–11 mg/24 hr
Cortisol metabolites (Michelakis)	7–17 mg/24 hr
FSH (follicle-stimulating hormone)	8–32 mouse uterine units/24 hours
Total estrogens	4–60 mcg/24 hr
Blood	
erythrocyte sedimentation rate	0–20 mm/hr (female)
serum PBI (protein-bound iodine)	3.8–8.0 mcg/dl
serum cholesterol	150–260 mg/dl
T_3 sponge uptake	40–60%
T_4	4.5–10.0 mcg/dl
T_3 index	0.8–1.2
T_3 by RIA (radioimmunoassay)	65–215 ng/dl
plasma FSH (follicle-stimulating hormone)	
female—pre-ovulatory	15–30 mIU/ml
male	5–40 mIU/ml
plasma ACTH by RIA	15–100 pg/ml
plasma cortisol by RIA	
8 AM	15–25 mcg/dl
5 PM	5–10 mcg/dl
plasma desoxycorticosterone	5–15 ng/dl
plasma total estrogens	
female—pre-ovulatory	45–200 pg/ml
male	10–80 pg/ml

plasma estradiol	
female—pre-ovulatory	15–75 pg/ml
plasma testosterone	
female	0.0–0.1 mcg/dl

Miscellaneous

I^{131} uptake (thyroid)	15–30% in 24 hr

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SUBJECT INDEX

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