CORTISONE THERAPY

MAINLY APPLIED TO THE RHEUMATIC DISEASES

BY

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"T[illegible] is book provides a veri[illegible]able treasure house not only for t[illegible] workers with a [illegible]inant interest in this field, but [illegible] for those gene[illegible]al practitioners and physicians [illegible]ecial interes[illegible]s lie outside rheumatology and [illegible]armly commend it."

[illegible]m the Foreword by Lord Cohen of Birkenhead.

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With a Foreword

by

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TO MY WIFE

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CORTISONE THERAPY

FOREWORD

SINCE cortisone was introduced for the treatment of rheumatoid arthritis nearly a decade ago, a vast literature has accumulated about the contribution it makes to the control and management of this widespread and so often crippling affliction. The overwhelming majority of the papers on this topic record personal impressions whose worth may be judged by the fact that by some cortisone is regarded as the "elixir vitae", by others as simply a "glorified aspirin". Controlled clinical trials in this country have done much to restore the balance between unbridled enthusiasm and therapeutic nihilism, and the time is now ripe for a reasoned appraisal of the place of cortisone and the newer steroid derivatives in treatment.

Few could be better qualified for this task than Dr. John Glyn who has had the advantage of working during the past few years with some of our most distinguished rheumatologists, and has himself taken part in the clinical trials of cortisone in this country and in America. From his personal experience and wide reading he provides in this monograph a comprehensive and judicial survey of the salient features of the chemistry and pharmacology of these steroids, and the practical problems of cortisone therapy, both oral and intra-articular. He deals fully with its place in the management of such collagen disorders as systemic lupus erythematosus, polyarteritis nodosa and dermatomyositis, and of allergic states in which, it may well be that cortisone derivatives will find their most effective role.

Dr. Glyn writes clearly and enthusiastically. Not all will approve unreservedly of all the opinions he expresses, and he recognizes that for the solution of many problems on which he gives his present tentative conclusions, further evidence is needed. But this book provides a veritable treasure-house not only for those workers with a dominant interest in this field, but also for those general practitioners, and physicians whose special interests lie outside rheumatology and allergy. I warmly commend it.

September, 1957 COHEN OF BIRKENHEAD

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SEVERAL chapters in this book have been adapted from a thesis submitted for the degree of Doctor of Medicine in the University of Cambridge, and I am grateful to the late Sir Lionel Whitby for permission to use this material.

I am very greatly indebted for the help, co-operation and advice I have received from numerous colleagues and chiefs in all the departments with which I have been associated. I would mention specifically Dr. W. S. C. Copeman, Dr. O. Savage and Dr. W. S. Tegner, because it was their guidance and enthusiasm which stimulated and then perpetuated my interest in the rheumatic diseases and in cortisone in particular.

I wish to express my gratitude to Dr. P. M. F. Bishop, who gave me invaluable help and encouragement in the construction of the original thesis, to Miss E. Gask, who performed the difficult task of creating order out of chaos by her secretarial assistance, and, finally, my most grateful thanks to Dr. A. Paton for much editorial advice. To my publishers I owe a special debt for their patience and forbearance.

J.G.

INTRODUCTION

THE discovery of cortisone more than eight years ago has created many more problems than it has solved in relation to the rheumatic diseases. Nevertheless it remains potentially one of the most fruitful discoveries in the history of medicine. During this period the pendulum of world opinion has swung from one extreme to the other, and the value of the steroid drugs in clinical medicine remains controversial.

A vast quantity of technical literature has appeared in the relatively short time since this epoch-making discovery, and it is quite impossible for any but the specialist to keep up with the field. It is the object of this book to interpret the available data in the light of the practical aspects of steroid therapy. While designed principally to help the general practitioner who is now able to treat and supervise patients taking steroid drugs, the book may prove of value to hospital residents and medical students who wish to know something of the problems—both theoretical and practical—associated with these hormones. I venture to hope that it may also provide a useful guide to those consultants in other specialities, for example dermatology and ophthalmology, whose therapeutic armamentarium has been strengthened by the advent of cortisone.

The major part of the book is concerned with the steroid treatment of the chronic rheumatic diseases, because these are common and were the original conditions in which cortisone was used. Moreover the author has been personally concerned with steroid therapy in this group of diseases since the early days. Another important consideration is that rheumatoid arthritis can serve as the typical example of a chronic disease, in which many of the problems of cortisone therapy may be expected to arise.

The first chapter describes the background to the discovery of the therapeutic effects of cortisone in September 1948, and some of the outstanding historical events in the ensuing years. Chapter 2 discusses the chemical nature of the steroid drugs, and this is followed in Chapter 3 by an account of their pharmacological properties. A clear understanding of these is a necessary prerequisite to the detailed discussion of the side-effects which follows. Chapter 4 is devoted to the practical aspects of therapy in rheumatoid arthritis, with extensive discussion of the selection, investigation and observation of patients to be treated, schedules of dosage, precautions to be taken and methods of overcoming most of the problems that are likely to be met. The indications for intra-articular injections are outlined in Chapter 5, and this is supplemented by an appendix showing anatomical approaches to the various joints. A comprehensive review of other conditions in which the drugs have been used is contained in Chapter 6. The final chapter

attempts to sum up the impact of cortisone on rheumatological practice and research and touches on some of the controversial issues raised by its discovery. Because much of the controversy has arisen from the imperfect nature of our methods for evaluating new treatments in the rheumatic diseases, this problem has received particular attention, and some examples of recommended procedures are included in the appendix. Recent developments and prospects for the future are discussed throughout the book.

Faced with the formidable task of abbreviating a mass of material into a small textbook, it is inevitable that there should be some degree of dogmatism, and that many dissenting opinions have had to be omitted. To the extent that such omissions reflect personal bias, I must bear full responsibility, recognising that it would be impossible to study a drug continuously for eight years without developing certain prejudices. Where however I am conscious of expressing unorthodox views I have tried to make this clear in the text.

NOTE.—Throughout the book cortisone and ACTH are not differentiated except where there are significant differences in their mode of action or administration. The terms "steroid," "hormone" and "cortisone" are to be taken as interchangeable and applicable collectively to all drugs used in treatment, unless the context makes it clear that a specific feature is under discussion.

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CHAPTER I

HISTORICAL REVIEW

RHEUMATOID arthritis was not clearly recognized as a pathological and clinical entity until approximately one hundred years ago. Until quite recently it has been regarded as a disease which progresses inexorably and irreversibly from its time of onset. Indeed a classical description of the disease in 1890 described it as ". . . one of the most intractable, obstinate and crippling diseases that can befall a human body". Others talked about the " great and lasting feebleness " which the disease produced, and one authority described it as being ". . . in one sense more malignant than cancer".

Through this fog of pessimism appeared one or two descriptions of cases which had unpredictably and inexplicably gone into remission, but the significance and potentialities of this phenomenon entirely escaped recognition. Even when in 1945 Ropes and Bauer clearly described the prolonged, or even lifelong, remissions which were characteristic of the natural history of the disease, their account was purely descriptive, and there was no hint that they were thinking in terms of therapeutic potentialities.

Hench has described how his concept of " potential reversibility " occurred to him in 1929 when one of his patients obtained dramatic relief of his symptoms and signs during an attack of jaundice. From this date he developed a growing conviction that this natural phenomenon could be used in the study of rheumatoid arthritis. This conviction was bolstered by 1934, when he had studied a further sixteen patients, all of whom responded well to interim attacks of jaundice which ". . . were sufficiently deep and characterized by a bilirubinæmia of the direct reacting type".

There followed the inevitable systematic search for " Nature's dramatic Antidote ", in which every conceivable constituent of bile was administered to groups of patients. Other sufferers even submitted to blood transfusions from jaundiced patients and a few were given hepatotoxic drugs in an effort to induce jaundice.

In retrospect, perhaps one of the most striking features of this work was the clear-sighted way in which Hench was able to recognize significant and relevant improvements, and distinguish them from the spontaneous remissions and exacerbations which so frequently occur when carrying out therapeutic trials in rheumatoid arthritis.

The relationship of pregnancy and the puerperal state to the clinical course of rheumatoid arthritis attracted but scant attention in early writings on the disease. Where it was mentioned at all, it was generally stated peremptorily that it had an adverse effect. However, sporadic references can be found in the writings of Garrod suggesting that it can sometimes check the progress of the disease for a short time.

It was again Hench and his co-workers at the Mayo Foundation who first began to appreciate the relative constancy with which patients improved during their pregnancy, only to relapse, in the majority of cases, in the puerperium.

The conviction grew that the remissions in jaundice were analagous to those in pregnancy, and indeed that they were probably due to the same agent. Hench started to explain these phenomena in terms of a hypothetical " Anti-rheumatic substance *X* " and stated that ". . . if the agent is a chemical substance it would appear that it is neither bilirubin nor a female sex hormone ".

Naturally the early searches for " substance *X* " centred around those metabolites whose concentration in the blood was known to increase in pregnancy and jaundice. As early as 1939 one finds references to cholesterol, ergosterol, sex hormones, bile acids and even Cortin (whole adrenal extract) in this connexion, but gradually the emphasis came to be laid on hormones, especially sex hormones. It was argued that since males get a similar degree of relief from jaundice, and since the pregnancy relief did not coincide with demonstrable increases in any of the known sex hormones, the responsible hormone must inevitably be common to both sexes.

Once interest was focused on jaundice and pregnancy it soon became evident that their ameliorative effects were not specific for rheumatoid arthritis but occurred in several other conditions, amongst which were asthma and other allergic diseases. Thus " substance *X* " came to be regarded as group specific rather than disease specific and the urgency for its identification increased.

Similarly the exclusiveness of pregnancy and jaundice as agents causing remissions began to be challenged. It was noted, for example, that typhoid vaccination with its febrile reaction was frequently, though not so dramatically, beneficial. Also starvation, surgical operations and even anæsthetics alone frequently produced a significant improvement. These observations were eventually to be given some logical basis by the concept of " stress reactions " propounded by Hans Selye in his famous monograph on the " general adaptation syndrome ".

With characteristic clarity of thought, Hench started to distinguish between the anatomical ravages of the disease, which he considered to be irreversible, and the physiological ravages which he regarded as potentially reversible. In illustration of this idea he evoked the metaphor of the house on fire, where the flames—which are extinguishable—represent the activity of the disease, whereas the ashes correspond to the irreversible joint changes. He was quite clear in his own mind that the substance he was searching for could have no effect on the latter.

The fortuitous association between Hench and Kendall ripened into a close collaboration between 1938 and 1948, during which time they discussed on numerous occasions the hypothetical possibilities as to the nature of " substance *X* ". Some of their earlier trials admittedly departed from the strictly hormone field, as for example when patients were treated with adrenal lecithin in an effort to reproduce the hyperlipæmia which often accompanies pregnancy and jaundice.

It was not apparently until 1941 that the decision was taken to try

17-hydroxy-11-dehydro-corticosterone (" Compound E " or Cortisone) when it became available. The rationale, in retrospect, seems a little tenuous although basically logical. In 1925, in noting the weakness, fatigue and low blood pressure common among patients with rheumatoid arthritis, Hench had briefly considered the adrenal gland as an ætiological factor; but when he came to make post-mortem examinations on two of his patients he could find no significant abnormality of the adrenal glands and consequently he laid aside the hypothesis.

Meanwhile Kendall had isolated Compounds E and F in 1934, and had chemically characterized these substances in 1937–38. Almost simultaneously they were isolated by Reichstein and by Wintersteiner and Pfiffner working independently of each other.

Ingle carried out animal experiments with these substances and found that they had a marked effect on muscular activity. They also influenced carbohydrate metabolism and increased physiological resistance to stress, cold and toxic substances such as typhoid vaccine. But the quantities in which they were available did not permit clinical experiments until considerably later.

Hench reports that when, at one of their meetings in 1941, Kendall told him of these physiological effects in animals, his mind reverted to his observations on the beneficial effects of typhoid vaccine on rheumatoid arthritis, and he wondered whether there could be any relationship between these two phenomena. He resolved at this point to try the effect of 17-hydroxy-11-dehydro-corticosterone as soon as it became available, which was not for another seven years.

In 1944 the Mayo Foundation produced small amounts of dehydrocorticosterone (Compound A). In 1945 this was produced in quantity by a commercial firm, Merck and Co. An attempt was made to use it in Addison's disease, where it was found to be useless. In 1946 there were only very small yields of 17-hydroxy-11-dehydro-corticosterone, and the process was laborious and extremely uneconomical. It was decided to abandon the method of production then in use in the Merck Laboratory and, in spite of the delay, to carry out more basic research into other methods of production. In 1947 several important technological developments emerged both from the Mayo Foundation and from Merck's.

By May 1948, the material was starting to become available in small but increasing amounts. Since then there have been immense and unpredictable improvements in production and, although a *total* synthesis is not yet practicable commercially, the basic limiting factor, namely shortage of bile, has been overcome by the use of other more readily available starting materials obtained from plant life.

Two fortuitous coincidences brought this painstaking research to a climax. For reasons that are still not clear, the investigators chose to use dosages of 100 mg./day. In 1948 this could have been considered a vastly excessive dose in relation to hormone requirements in other conditions. Had they used a smaller dose we now know there would probably not have been any result, and the discovery of cortisone might have been delayed for many years.

Secondly, the size of the crystals in their preparation happened to

be absorbed at approximately the right speed. Had they been larger, absorption would have been slower and the clinical remissions far less dramatic.

In August 1948 a patient with rheumatoid arthritis in the Mayo Foundation failed to get jaundice or relief following lactophenin administration. In September 1948 a letter was written to the Merck Company requesting enough 17-hydroxy-11-dehydro-corticosterone to treat this one patient. On 21st September, 1948, the first injection of cortisone crystals was given to this patient with the dramatic results which are well known. The remainder of this book is, in effect, an account of the results of this injection.

September 1948—Present Day

The discovery of the clinical potentialities of cortisone precipitated a flood of clinical and scientific research, which increases year by year as supplies become more easily available.

The volume and diversity of this research makes it inconvenient to review the progress chronologically. It will therefore be considered under the following headings:

1. **Premature Publicity.** The commendable caution with which Hench and his colleagues introduced their discovery as an " Investigative Weapon " contrasts markedly with the premature and over-enthusiastic reports which appeared elsewhere, not only in medical journals, but also in the lay press.

It provides an interesting commentary on the interrelationship of economic and scientific factors in this type of research. Hench's original intention was to carry out an intensive study of the drug's clinical applications before announcing his discovery in 1950, or even 1951. However, the cost of producing the drug, even in the quantities necessary for a small clinical trial, was so prohibitive that the commercial firm involved was forced to demand corroborative evidence from independent investigators before setting up the machinery for production.

Once the investigation was thus divided up, it did not take the lay press long to discover the secret, and to make all manner of sensational and unjustified claims of a *cure* for arthritis. The early and unbalanced enthusiasm thus engendered was undoubtedly responsible for the subsequent vicissitudes in the reputation of the drug.

2. **The Supply Position.** The limitations imposed by the problems of production in the early days—and of distribution outside the " Hard Currency " areas, until very recently—have had a profound bearing on the different experiences with the drug on either side of the Atlantic.

Great Britain (in common with most other European countries) had until 1953 a very small allocation of cortisone, and partly for this reason nearly all of it was issued to a few selected centres for research purposes. Even since 1953 the supply position has only slowly improved and it did not become generally available to practitioners until 5th December, 1955.

Two important results have stemmed from this. Firstly, our cases

have been very carefully " screened " before selection, and patients who—within the limitation of our knowledge—were likely to develop serious side-effects were eliminated.

Secondly, the drug was given with extremely careful clinical and laboratory control, so that side-effects could be detected and dealt with in their earliest phases.

By contrast, in the United States, as soon as supplies became available, they were distributed through ordinary commercial channels so that economic and personal factors frequently took precedence over purely clinical ones in case selection.

Furthermore, much of it was administered by clinicians who had not had the opportunity of gaining experience either in the rheumatic diseases or in the special problems which are implicit in hormone therapy. These factors combined with dosage regimes which we now know have been grossly excessive were responsible for an appalling legacy of side effects in some parts of the United States.

Because of the supply situation we were therefore able to profit from the earlier experiences of our American colleagues and our incidence of dangerous complication has been correspondingly less.

Those who were responsible for dealing with these problems naturally developed antipathetic opinions about the use of such potent drugs, and much of the current controversy probably stems from the emotionally charged views which arose from these experiences.

3. **The Search for Analogues and the Discovery of the Specificity of Cortisone.** The discovery of any new drug is generally followed by a search for simpler, cheaper, safer or more effective analogues. In the case of cortisone this search was even more extensive than usual, for which one can postulate the following reasons.

(*a*) It represented a completely new approach to therapy in rheumatoid arthritis, and proved conclusively that the concept of " Potential Reversibility " was valid.

(*b*) It was stated categorically by experienced chemists that it would never be possible to produce a fraction of the quantity necessary to meet clinical requirements, and that as a result the practical application of the discovery would always be limited by economic and technical factors.

(*c*) Cosmetic and other serious side-effects were caused by cortisone.

(*d*) There was complete ignorance of the vital pharmacological action of cortisone. This enabled workers to take an extremely catholic approach to the problem. As each metabolic effect revealed itself, any other substance known to have a similar action was sure to be given a clinical trial in case this was the " vital action " by which cortisone acted therapeutically.

It took a long time before the remarkable specificity of cortisone and hydrocortisone was appreciated.

The specific characteristics were described in 1950, and seven years later they have not been successfully challenged, despite the prodigious combined efforts of chemists and clinicians to produce a simple and effective analogue which could be made at a reasonable price. These

efforts were usually directed at modification of the steroid nucleus itself, and in a recent book Hench lists more than fifty variants, all of which have now passed into the limbo of obscurity.

It is notable, however, that most of them were originally thrust into prominence by the premature and exaggerated claims of enthusiastic workers who did not appreciate that the natural history of rheumatoid arthritis is to show cyclical variations in activity. This would not have been so serious were it not for the fact that each claim necessitated at least one, and usually several, laboriously planned clinical trials before it could be refuted.

Apart from the waste of time and money thus entailed, there were humanitarian factors to be considered, since most of these steroids were dissolved, for technical reasons, in ethyl oleate, and this appears to be a highly irritant oil, causing severe local tenderness in all cases and large abscesses in those who were less fortunate.

Apart from steroid analogues, there were very many attempts to stimulate the suprarenal cortex artificially, and without actually using corticotrophin. Drugs used for this purpose included adrenalin, insulin, liquorice extract, adenylic acid, ascorbic acid, dehydro-ascorbic acid, and many others. There was another vogue for treating patients with daily electro-convulsion therapy in an effort to stimulate the pituitary-adrenal axis via the hypothalamus. Finally, one Scandinavian team claimed excellent results from intra-gluteal implants of calves' anterior pituitaries, especially in patients under forty.

None of these claims has withstood the tests of time, but they remain of considerable historical interest.

4. **" Cortisone Sparers ".** Running parallel with these disappointments have been the efforts of those who have searched for " cortisone sparers ", i.e., drugs which would either potentiate the effect of a given dose of cortisone, or enable the same effect to be obtained with a smaller and therefore less toxic dose.

These efforts have taken one of three main forms: in the first, cortisone has been combined with another, recognized analgesic or " anti-rheumatic " drug, in the hopes that the therapeutic effects will be additive whilst their side-effects will not. To this end, cortisone has been combined with salicylates, with gold, and more recently with phenylbutazone.

Whilst in individual cases these combinations have proved useful in reducing the dose of cortisone below the toxicity level, it is a potentially dangerous approach. This is especially so in the case of gold, since the cortisone may mask the early toxic effects of the gold, and so allow the patient to accumulate high tissue concentrations with a sense of false security, until for one reason or another the artificial cortisone suppression is removed. Furthermore, at least one observer has produced evidence to show that gold and cortisone are mutually antagonistic substances.

Phenylbutazone shares with cortisone the propensity of sodium and water retention; consequently they should not be used together in any patient who exhibits this tendency. Similarly both drugs share the

common danger of causing peptic ulcers or acute gastric erosions with hæmatemesis. In fact there are relatively few cases where they can safely be given together except in very small doses.

By contrast, salicylates can be given routinely with cortisone; and it is certainly possible and desirable on occasions to diminish the requirements of cortisone by the judicious supplementary use of aspirin. Indeed it is a common habit to allow intelligent patients to adjust their own aspirin consumption according to their varying symptomatic requirements, and to use the record so obtained as one of the factors in assessing the correct maintenance dose of cortisone.

The second approach to the problem has been to try to potentiate the action of a given dose of cortisone, either by increasing its peripheral utilization or by delaying its breakdown in the liver. Small doses of insulin were claimed to work by the former method, and large doses of para-amino-benzoic acid by the second. This explanation is unlikely to be correct, however, since cortisone produces such a marked increase in resistance that insulin is probably quite inert metabolically in the doses in which it was advocated. It is no longer used in practice.

Para-amino-benzoic acid is still recommended by at least one group of workers in the United States, but we have been quite unable to reproduce their claims of substantial cuts in cortisone requirements in this country. In any event it is a practical problem of some significance to persuade patients to swallow 12 grammes of an extremely unpleasant medicine every day before they take their cortisone.

Another attempt on the problem was made in the early days by invoking a pituitary " feed-back " mechanism. It was hoped that by administering œstrogens simultaneously with the cortisone, the output of some of the other " trophic " hormones of the anterior pituitary would be diminished, thereby decreasing the endocrine side-effects. There is no evidence that this occurred in practice, and the method has been abandoned. Large doses of thyroid have been given on the same principle, and with the same disappointing results.

5. **The Development of Prophylactic Measures.** Perhaps the most logical and hopeful of the attacks on cortisone toxicity has been the use of routine prophylactic measures to counteract those essentially physiological actions of cortisone which become an embarrassment with prolonged administration of the drug.

For example, cortisone causes sodium retention and potassium excretion, and many clinicians recommend routine salt restriction and the daily administration of 3–4 g. of a potassium salt such as potassium nitrate or chloride.

Similarly, the routine administration of testosterone will reverse to some extent the catabolic effect which cortisone has on the body nitrogen and calcium. This, however, is expensive, and the complementary virilizing effects of the two drugs make it impractical to use in most female patients.

Diet is naturally an important factor in counteracting the tendency of these patients to become pathologically obese. Furthermore, a group in California have published some interesting metabolic studies in

which they prove that certain modifications of the diet can substantially reduce the urinary 17-ketosteroid output from a given dose of cortisone, with a corresponding reduction in the unwanted side-effects. The details of their diet would not be easy to carry out in practice without the aid of a special dietetic department. However, in principle it represents the type of diet at which cortisone intolerant patients should aim. (See Chap. 4).

6. **Methods of Administration.** Several other fundamental changes have occurred in the course of the past seven years, for example, the discovery that cortisone, far from being destroyed by gastric and intestinal digestion, is absorbed with its action unimpaired. In fact it was found to be absorbed more rapidly and regularly than the intramuscular injections used hitherto.

In the early days following this discovery it was customary to ask patients to swallow the micro-crystalline suspension as prepared for injection, but the excessively bitter taste was impossible to mask with the customary flavouring agents and the patients found it well-nigh intolerable. However within a very few months the manufacturers had succeeded in preparing tablets, and it is in this simple form that it is now prescribed.

No long-term treatment is pleasant when it means daily injections of a fairly bulky preparation, but the micro-crystalline steroids seemed to suffer from two additional hazards of their own—namely: their slowness and irregularity of absorption and their terrifying propensity for causing large buttock abscesses following injection techniques which were above reproach. These abscesses were usually sterile on culture but were extremely obstinate in their response to the usual treatments.

7. **Dosage Regimes.** Another important change has been in our conception of dosage. This will be discussed in detail later and it is sufficient to note here that it used to be routine to commence a patient on about 300 mg. daily, and then gradually to reduce the dose to a maintenance level of about 100 mg. Nowadays it is very rare to start treatment at more than 100 mg. a day and the clinician's constant aim is to get down to the lowest possible dose compatible with the patient's *reasonable* comfort.

Many different dosage schedules are reviewed by Hench in one of his latest publications. Most of them are now obsolete, but he does stress repeatedly that the dosage schedule must be " tailored " to fit the requirements of the individual patient, and this refers not only to the total amount of the drug he takes in the course of a day, but also how he divides up the dosage in relation to his symptoms, which are usually cyclical.

The other great mistake which was not appreciated for two or three years was to vary the dose excessively from day to day. We now know that the tissues seem to adjust themselves to various blood levels of circulating hormones, and sudden diminutions of these levels can cause a feeling of profound illness.

8. **Refinements in the preparation of Corticotrophin.** In the early days