PHILIP S. HENCH

The reversibility of certain rheumatic and non-rheumatic conditions by the use of cortisone or of the pituitary adrenocorticotropic hormone

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It may be appropriate to discuss in this Nobel Lecture three general aspects of cortisone and pituitary adrenocorticotropic hormone (ACTH): (1) the development of the theory which eventually led to the use of cortisone and ACTH in rheumatic and certain other conditions; this I shall do in some detail, giving certain data not published heretofore; (2) the present status of cortisone and ACTH in general medicine; this topic I shall discuss summarily in view of the several current reports thereon; and (3) some major requirements for the orderly development of cortisone and ACTH as therapeutic agents; this aspect will be touched upon briefly.

Development of the Theory which Led to the Use of Cortisone and ACTH in Rheumatic Diseases

Previous opinions on the prognosis of rheumatoid arthritis. The anatomic and clinical identity of what we now call rheumatoid arthritis was established fairly clearly about 100 years ago. During the next 75 years medical writers emphasized the distressing chronicity of this condition.

Rheumatoid arthritis was called "one of the most intractable, obstinate, and crippling diseases that can befall the human body" (Lane and Griffiths, 1890). Distinguished English clinicians were concerned by "the great and lasting feebleness" (Garrod, 1859) which the disease produced and by its "cases of ruin and despair, in one sense more malignant than cancer" (Spender, 1889).

A contrasting feature of rheumatoid arthritis, that of its occasional remissions, attracted the attention of some writers (Garrod, 1876; Osler, 1892; Jones, 1909). But relatively complete remissions were so uncommon or so unpredictable that they were regarded as medical curiosities, the sponta-

neous appearance or therapeutic induction of which was hardly to be expected. This air of pessimism regarding the rheumatic disease in general and rheumatoid arthritis in particular still finds expression in some of the modern writings and texts.

Ameliorating effect of jaundice on rheumatoid arthritis. It was in this gloomy tradition that, beginning about 1923, I served my rheumatologic apprenticeship. But on April 1, 1929, a 65-year old patient at the Mayo Clinic told me an unusual story. A few days before that date he was painfully affected with rheumatoid arthritis, as he had been for four years. Then jaundice suddenly developed, and within a week most of his arthritic manifestations had disappeared. The jaundice lasted five weeks but the rheumatoid arthritis did not relapse until several weeks after the jaundice had disappeared.

The thought occurred: Instead of being relentlessly progressive, this disease, rheumatoid arthritis, may be potentially reversible, more so than we have believed, perhaps rapidly so.

During the next five years (1929 to 1934) observations were made on 16 patients with chronic arthritis or fibrositis in whom jaundice of different types and degrees developed[39d,e]. If the jaundice was deep enough and was characterized by bilirubinemia of the "direct-reacting type", the rheumatic symptoms quickly diminished or disappeared for varying lengths of time (days to months) and then gradually returned.

Early speculations regarding the ameliorating agent of jaundice. The fact that, contrary to general opinion, rheumatoid arthritis was potentially reversible, and rapidly so, thus became increasingly apparents[39f,g,k]. But what agent was responsible for the sudden reversibility of this disease during hepatitis with jaundice? The dominant feature of visible jaundice suggested that a biliary constituent might be responsible[39d,e]. Was the amelioration of rheumatoid arthritis the result of a temporary excess in the blood and bodily tissues, of a normal biliary constituent such as bilirubin or bile acids, or of an abnormal substance produced during jaundice, such as an autolysate of the liver or of some other tissue?[39d,e]. It seemed reasonable to believe that such striking relief from rheumatoid arthritis was effected by some substance which was normal to the human organism rather than by an abnormal material[39f,h]. Therefore the hope was expressed "that jaundice provides to the general circulation, not an abnormal product but a normal constituent, adequate amounts of which perhaps the arthritic patient did not have"[39f,h].

But because the ameliorating effect of jaundice sometimes lasted several weeks after the values for serum bilirubin in blood had returned to normal it did not seem likely that bile pigments were responsible[39f,h].

Therapeutic implications. The therapeutic implications inherent in these observations were recognized, and the hope was expressed that further studies might lead to the discovery of the responsible agent which might some day be provided at will[39e-h]. "A study of the phenomenon may enhance our knowledge of the pathogenesis of these [rheumatic] diseases and may lead to some superior method of treatment"[39j].

Attempts to reproduce the phenomenon of relief by using substances related to jaundice and the liver. A search for the ameliorating agent, "Nature's dramatic antidote"[39g] was begun. To test the validity of the conjectures mentioned above, and in an attempt to reproduce the phenomenon of relief which may occur during spontaneous jaundice, various methods were employed[39g,h,j,k]. Volunteers with rheumatoid arthritis were given bile salts by mouth, a derivative of a bile acid (decholin) orally and intravenously, liver extracts parenterally, ox bile by proctoclysis, and large amounts of human bile by stomach tube. A few other rheumatoid volunteers underwent transfusion with blood from highly jaundiced patients. But these procedures had no significant antirheumatic effect. One rather desperate rheumatoid patient permitted me to give her toluylene diamine by mouth; unfortunately and surprisingly, the jaundice induced thereby was of the hemolytic type and did not induce a remission[39h]. Then, to other volunteers with rheumatoid arthritis, bilirubin was given intravenously alone, or in combination with decholin after the method of Thompson and Wyatt (1937). Although the patients experienced marked hyperbilirubinemia and became strikingly pigmented, the results were negative or at least quite inferior to the effects of spontaneous jaundice[39g,h].

The ineffectiveness of these various substances, the ones which were most obviously related to jaundice, strengthened an earlier suspicion that, despite the dominant feature of visible jaundice, the antirheumatic "substance X"[39h] might be "an extrahepatic substance found or activated elsewhere than in the liver as the indirect result of jaundice"[39g,j], or at any rate, that it might be some substance not necessarily related to jaundice. Thus it was stated, "Among other phenomena, pregnancy, which seems to have little or nothing to do with bilirubin, often provokes a similarly effective if less dramatic

remission in [rheumatoid] arthritis... If this represents a chemical control, I wonder if Nature in the last analysis has more than one way of controlling the arthritic process. There should be some common denominator between the two reactions and, off hand, bilirubin seems to be excluded"[39h].

Ameliorating effect of pregnancy. For many years observers, noting the greater incidence of rheumatoid arthritis among women, had speculated as to possible relationships between this disease and the menses, pregnancy, and the postpartum state. The literature of the past century contains scattered references to the subject, generally only a sentence here or a paragraph there. Earlier writers generally believed that pregnancy and especially the puerperal state exerted an adverse effect on patients with rheumatoid arthritis (Trousseau, 1871; Charcot, 1881; Bannatyne, 1896; Strangeways and Burt, 1907). But it was also occasionally noted that pregnancy sometimes temporarily checked the disease (Garrod, 1890; Llewellyn, 1927). In summary, the conflicting and confusing opinions stated that rheumatoid arthritis may be precipitated by, or first appear during, pregnancy; that it may be aggravated during, or relieved partially or completely by pregnancy; or that the disease is unaffected by pregnancy but aggravated by the postpartum state. No critical investigation appears to have been undertaken to clarify these confusions.

At the Mayo Clinic we saw, not infrequently, patients who had become pregnant during the course of their rheumatoid arthritis. It was observed that most of them noted, not long after the onset of pregnancy, an undramatic and slowly progressive development of relief from their arthritic disability. Prior to 1929 this phenomenon did not engage our attention except for the matter of recording it in the appropriate records. But after 1931, records of these cases were more carefully made and assembled by my colleague, Dr. Charles Slocumb, and me, because of my growing belief that this phenomenon of relief was analogous to, if not identical with, that which may occur during jaundice[39d,f], and that the same agent might be responsible for the relief both during pregnancy and jaundice, although the mechanism for developing the agent might be different[39h].

Relationship between the antirheumatic agent of jaundice and that of pregnancy. As a result of observations on the effect of 34 pregnancies on 20 patients with rheumatoid arthritis the pattern of the articular relief during pregnancy was described in 1938[39i]. A more extensive study was summarized in

1949[39m]. Regarding a possible relationship between the antirheumatic substance X of jaundice and that of pregnancy, the following tentative conclusion was reached: "It does not seem illogical to suppose that the agents responsible for both these phenomena are closely related, perhaps identical, and if the agent is a chemical substance, it would appear that it is neither bilirubin nor a strictly female sex hormone"[39h,i].

Could substance X be a bisexual hormone? The comment continued: "It is interesting to note the close chemical relationship between such diverse substances as cholesterol [which may increase in blood in both jaundice and pregnancy], ergosterol, the precursor of vitamin D [which was, in 1938, considered by some to be useful in rheumatoid arthritis], some of the sex hormones [which were occasionally given to rheumatoid patients with negative or equivocal results], cortin, and bile acids. Further studies are in progress to discover if possible, the responsible agents for therapeutic purposes. If the potent common denominator of these two phenomena - the ameliorating effects of pregnancy and of jaundice - can be discovered, progress in treatment may be expected"[39i].

One of the chief biologic changes related to pregnancy was known to be a marked increase in the bodily concentration of certain hormones. Thus it was the studies on the ameliorating effect of pregnancy which led to a transfer of interest from some biliary substance to a consideration of some hormone as the possible substance X. Although cortin (whole adrenal extract) was one of the glandular extracts which we listed for consideration in 1938 we did not use it till later.

But which (if any) hormone might substance X be? Despite the dominant feature of pregnancy the following facts seemed to speak against the likelihood that the unknown antirheumatic agent was a unisexual hormone, that is, a female hormone or one strictly related to pregnancy: (1) jaundiced rheumatoid males obtained the same relief as non-jaundiced pregnant females; (2) the pattern of relief during pregnancy did not clearly coincide with the time periods during which any one of the then known female sex hormones was reported to be increased; (3) certain female sex hormones, administered from time to time to a few rheumatoid patients by various workers including my colleague, Dr. Charles Slocumb, had produced no striking or consistent relief. Hence it was conjectured that if substance X was a hormone it was not a unisexual (female) hormone but a bisexual one[39i].

Specificity of these phenomena. Changing views were held as to the specificity of the effects of jaundice and pregnancy. Among our first patients relieved by jaundice or pregnancy were a few with fibrositis, intermittent hydrarthrosis, or sometimes sciatica, as well as those with rheumatoid arthritis. Therefore the phenomenon of relief was at first (1934) regarded as "probably non specific", at least not specific for rheumatoid arthritis alone[39e,f].

Later (1938) the phenomenon was tentatively regarded as being "relatively specific for rheumatoid arthritis and fibrositis"[39h,j]. Then (1940) it was noted that patients with hay fever and severe asthma, egg sensitivity or migraine, were sometimes relieved by intercurrent jaundice; in other words hepatitis with jaundice appeared to "invoke an anti-allergic as well as an antirheumatic reaction"[39k]. Finally, data were collected which suggested that patients with psoriasis or psoriatic arthritis, asthma, migraine, hay fever, Addison's disease, and myasthenia gravis were sometimes relieved during pregnancy and/or jaundice[39m]. Therefore the phenomenon of relief by the hypothetical common denominator of jaundice and pregnancy came to be regarded as "group-specific rather than disease-specific"[39k,m]. This of course enhanced greatly the potential importance of substance X.

Related phenomena. Through the years during which these studies on the effects of jaundice and pregnancy on several diseases, but particularly on rheumatoid arthritis, were being pursued, it was noted that somewhat similar, though less dramatic, symptomatic remissions could be induced, occasionally by reactions to typhoid vaccine[39a,k,m], not infrequently by almost any surgical operation[39d,k,m], and also by short periods of starvation[39k,m]. We suspected that anesthesia alone might be an important factor in the production of the transient postoperative relief which followed diverse surgical procedures on patients with rheumatoid arthritis[39d,m]. My colleague, Dr. Slocumb, confirmed this fact, producing certain degrees of articular improvement by giving various anesthetic agents alone to several rheumatoid volunteers[86].

The phenomena of relief by these various other procedures were regarded as probably related somehow to the more familiar phenomena induced by jaundice or pregnancy[39d,f,k]. But for a long time speculations thereon did not provide a clue as to the probable identity of substance X.

Recapitulation of conclusions and conjectures (1929-1940). In summary, the following conclusions and conjectures were arrived at from 1929 to 1940, partly as a result of various clinical observations and partly as the result of

numerous experimental failures*. In passing, it may be worth mentioning that the development of the theory which eventually led us to the use of cortisone and ACTH in rheumatic and other conditions was guided as much by our failures to induce experimental remissions with certain particular substances as it was by interrelating the clinical observations.

It was decided that: (1)rheumatoid arthritis was not necessarily a relentless progressive disease but was potentially reversible; (2) there developed during jaundice and pregnancy (perhaps also during typhoid vaccine reactions, starvation, and anesthesia) an antirheumatic "substance X"; (3) if non-jaundiced pregnant women and jaundiced males were relieved in a similar manner, as seemed likely, substance X was not a unisexual (female) hormone nor the product of a damaged liver; (4) substance X was probably a biologic compound[39h,m] which is normal to the human organism[39f,h], one which is specific in nature and function[39h,m]; and (5) in view of the ameliorating effect both of pregnancy and of jaundice, substance X might be a bisexual hormone.

Could substance X be an adrenal hormone? Prior to 1938 my conferences with Dr. Kenda11 concerning the possible nature of substance X were irregular, infrequent, and casual. But thereafter he became my chief collaborator, and my conferences with him became more and more frequent. As we tried, on innumerable occasions from 1938 to 1948, to conjecture what might be the chemical nature of substance X, neither of us knew that he and his associates, working on compound E (the adrenal cortical substance, 17-hydroxy-11-dehydrocorticosterone) in his laboratory a few yards away, were at that very moment isolating, identifying, and preparing to synthesize "substance X" or a reasonable facsimile thereof.**

It would not be proper to infer that my confidence in the validity of these developing concepts was constant and unwavering. One was often dealing only with subtle suggestions, and it was frankly recognized that one or more

* During these several early years (1929 to 1940) in which the above-mentioned clinical observations were made and these ideas were being formulated, I had the council and aid of many colleagues at the Mayo Clinic, chief of whom were my departmental colleague, Charles H. Slocumb, M.D., who became associated with me in 1934, and Edward C. Kendall, Ph.D., of the Department of Biochemistry.

* * It is the privilege of Drs. Kendall and Reichstein to describe on this occasion, in their own Nobel Lectures, the isolation, identification, and production of the substance which was called compound E by Kendall, substance Fa by Reichstein and his associates, and compound F by Wintersteiner and Pfiffner.

of the main presumptions were not based on certain knowledge or facts, but were the (seemingly) logical development of some other presumption which, however, reasonable it might appear to be, might be erroneous. Hence, other possibilities were entertained from time to time and occasional excursions into the empiric were indulged in. In 1938 Dr. Slocumb and I gave to a few patients with rheumatoid arthritis, adrenal lecithin prepared for us by E. C. Kendall and B. F. McKenzie. We administered it, not as an adrenal product *per se,* but in an attempt to produce hyperlipemia which often accompanies jaundice or pregnancy. No significant relief resulted.

Decision to administer compound E of Kendall. During one of our conferences in January, 1941, Dr. Kendall and I decided to administer to rheumatoid patients the adrenal cortical substance, 17-hydroxy-II-dehydrocorticosterone, whenever it might become available. The reasoning behind this joint decision was fragile, but it was logical in the light of what we knew then and know now. Sixteen years previously, in 1925, the weakness, fatigue, and low blood pressure common among patients with rheumatoid arthritis, which we then called "chronic infectious arthritis", suggested to me that in connection with, or in addition to, a supposed factor of infection, secondary ‘metabolic changes were present, and that the adrenal glands might somehow be involved in this diseases[39b,c]. But the postmortem examination, in 1925, of the adrenal glands of two patients with rheumatoid arthritis lent no support to the vague suspicion regarding an adrenal factor[39c], and the notion, though not forgotten, was laid aside.

In our conference of January, 1941, Dr. Kendall (with whom I had previously discussed not only the above-mentioned vague notion of an adrenal factor in rheumatoid arthritis but also the striking if transient remissions sometimes induced by reactions to typhoid vaccine) remarked-that his compound E increased the resistance of animals against reactions to typhoid vaccine. Kendall’s compound E[56,57,67] (substance Fa of Reichstein[79]) was being separated in small amounts from the adrenal glands of animals but it had not yet been tested in any human disease. Might it be useful against rheumatoid arthritis? The decision to try it out was recorded in my pocket notebook. But we did not know then that almost eight years would elapse before there would be enough of this adrenocortical substance to administer to a rheumatoid patient. Our plan to use it remained attractive through the several years of waiting.

In lieu of this. hormone, Slocumb and I gave, in 1941, Kendall’s adrenal

cortex extract, "cortin", to three patients with rheumatoid arthritis, without impressive results[42]. With none of Kendall's compound E or any other likely product available to us we then (1941 and 1942; 1946 to 1948) produced in a few arthritis volunteers jaundice induced by the oral use of lactophenin after the method of Hanssen (1942). Temporary remissions were induced but we could not identify the responsible agent[39m].

First use of Kendall's compound E in rheumatoid arthritis. In August, 1948, we tried to relieve a woman, badly crippled with rheumatoid arthritis, by giving lactophenin orally to induce jaundice. But no jaundice developed. We then decided to try compound E (Kendall) if it was available. Our earlier conjecture that substance X might be an adrenal hormone had meanwhile become strengthened by the observation of others[10,26,99,100,105,106,108] that some of the seemingly diverse agents which often temporarily relieved arthritic patients (foreign protein reactions, starvation, various surgical operations) were now known to be capable of stimulating the adrenal cortex. But despite our sustained desire to use this hormone whenever it might be available, we had no firm conviction, only the hope, that this compound might be substance X.

A letter[391] requesting enough of Kendall's compound E for one patient was sent on September 4, 1948, to Merck & Co., Inc., whose research chemists (chiefly Dr. L. H. Sarett[84]), working in collaboration with Dr. Kendall and his associates, had finally succeeded in making a small amount of this substance. The letter concluded: "We know that there is a potentially provokable mechanism [for the reversibility of rheumatoid arthritis] which is activated by pregnancy and jaundice very rapidly, by jaundice for example within three days... Therefore if any adrenal compound is of real significance in rheumatoid arthritis we would expect to see some results within a very few days." A small supply of Kendall's compound E was soon received from Drs. Randolph Major, Vice President, and James Carlisle, Medical Director of Merck & Co., Inc.

Dr. Kendall and I decided to use for this first rheumatoid patient daily doses of 100 mg intramuscularly, so that we might not commit the error of underdosage. Thus, on September 21, 1948, Dr. Slocumb began to administer to the above-mentioned patient daily doses of 100 mg of compound E (not the acetate) in the form of a crystalline suspension in saline solution. Within three days the patient was markedly improved and continued to improve until the daily dose was reduced to 25 mg.

Because of very limited supplies and the difficulties which were encountered in the preparation of the early suspensions, only four more patients were given compound E (which Dr. Kendall and I later renamed "cortisone") from September, 1948, to January, 1949. The preparation of the suspensions of compound E for intramuscular injection presented many problems which, step by step during these months, were solved by Dr. Kendall, who has discussed them elsewhere[56,57].

In January, 1949, we requested a supply of ACTH from Dr. John R. Mote, then Director of Laboratories of Armour & Co. We first administered it on February 8, 1949, to a patient with rheumatoid arthritis. Thereafter cortisone (Merck), or ACTH (Armour) or both were given by my associates Drs. Slocumb and Polley, and by our assistants to a series of patients with severe or moderately severe rheumatoid arthritis. The first report of results was presented April 20, 1949, by Hench, Kendall, Slocumb and Polley[40]. Dr. Randall Sprague had become our advisor in metabolic procedures and carried out the metabolic studies which were made in some of our cases by himself in collaboration with Drs. Power, Mason, Albert, and Mathieson[94].

The Present Status of Cortisone and ACTH in General Medicine

General results of cortisone or ACTH in rheumatoid arthritis

Clinical effects. To date several thousand patients with rheumatoid arthritis in various parts of the world have received either cortisone, generally cortisone acetate, or ACTH, daily for periods varying from only a few days to many months. The results obtained elsewhere[3-8,17,22,24,28,50,52-54,60,64,69,78,82,91,92,101,102] are in agreement with those reported from the Mayo Clinic[39,40-45,107].

In practically all cases most of the symptoms have markedly and quickly diminished during the use of either hormone. Because the clinical results from ACTH are essentially similar to those from cortisone it is assumed that ACTH, when injected intramuscularly, stimulates patients with responsive adrenals to increase the production of their own cortisone, or a similar steroid hormone such as 17-hydroxycorticosterone (Kendall's compound F)*.

* This has since been named "hydrocortisone".

When either hormone is given, there is a diminution, first of the subjective phenomena (stiffness, soreness, tenderness), later of the objective features (fever if present, swelling, flexion contractures if not too long established, size of rheumatoid nodules, and enlarged lymph nodes). A sense of well-being, increased psychomotor activity, and increased appetite and weight commonly develop.

Laboratory abnormalities tend to diminish. Sedimentation rates generally decrease, often rapidly. Hemoglobin concentrations may increase and hyperglobulinemia usually decreases. Urinary 17-ketosteroids generally diminish during the daily use of 100 mg doses of cortisone, increase during the use of ACTH[42,66,94]. Either hormone increases the excretion of corticosteroids in urine. Urinary amino acids increase during remissions induced by cortisone or ACTH as they do during spontaneous remissions or those related to pregnancy or jaundice[9,50]. The hormones may alter the alpha waves in electroencephalograms[6,49,78]. They do not prevent formation of antibodies, nor alter agglutinins to sensitized red sheep cells present in sera of rheumatoid patient[98].

Subjective relief may be marked but incomplete, almost complete or complete. Objective features usually do not disappear entirely: some fusiform thickening or painless articular bogginess may remain to show that the disease is suppressed rather than cured. Residual architectural damage to cartilage and bone remains unaffected. Articular biopsies of synovia, carried out before and at various times during the use of these hormones, have revealed varying degrees of improvements[3,42].

Results of hormonal discontinuance. Relief of symptoms has usually lasted as long as the hormones were given. But thereafter relapses have generally occurred: usually within one or two months, occasionally more promptly and severely (rebound relapses)[42]. But a number of patients have retained much, sometimes almost all, of their relief for several months without the aid of the hormones[42]. A few other patients have experienced a short relapse for about a month, then regained much of their previous improvement. The question arises whether these posthormonal remissions were spontaneous and coincidental or induced by the previous hormonal usage.

Undesirable physiologic effects ("side effects") of cortisone and ACTH. The doses of hormones required to suppress rheumatoid arthritis are relatively high compared to doses which protect addisonian patients (or patients with

adrenal insufficiency)*. Often these doses are well tolerated, especially if given for only a few weeks; sometimes they are not, in which case the consequences of hypercortisonism develop, and any one or more of a variety of effects may occur. Some of these are of little importance; others are of greater consequence and may provide certain hazards to certain patients[40-45,94].

Side effects encountered fairly frequently have been mild irritability with increased psychomotor activity, an initial retention, generally mild, of sodium chloride and water, producing fluctuant weight with or without visible pretibial edema; mild hypertrichosis, acneiform eruption or rounding of the face. Fluid retention if it develops, is usually mild, generally lasts only a few days and may then disappear even though the dosage of hormone is not altered. The doses currently employed do not as a rule produce deficits of electrolytes or nitrogen, at least in persons allowed eat at will. Certain rare or rather rare side effects are of special interest[6-8,14,28,50,69,72,78,82,94,102]: transient renal glycosuria or significant reduction of carbohydrate tolerance[6,42,51,93]; hypopotassemic hypochloremic alkalosis[42,94]; transient major alterations of psyche which may develop for a few days, generally in persons with markedly disturbed personality patterns, or with prepsychotic or psychotic dispositions[49,78,81]; and spontaneous fractures occurring in elderly osteoporotic persons usually after excessive physical activity. Significant interference with wound healing has occurred rarely in patients receiving the usual doses employed. So far all the side effects observed by us and others have been reversible and have disappeared when the dosage was lowered sufficiently, or the use of hormone discontinued.

The side effects have been listed and discussed in detail elsewhere[42,45,94]. Physicians who would use these hormones should become familiar with these possible side effects and-with certain measures devised for their prevention, modification or control.

Because of their potential effects, cortisone or ACTH should be used with caution in the following: hypertensive cardiovascular disease, diabetes mellitus[6,42,51,94,] tuberculosis, old rheumatic carditis with decompensation[68,69,94,102], latent or frank psychoses[81], marked osteoporosis associated with senility or with rheumatoid arthritis[102], and peptic ulcers[32,83].

Certain measures have been devised to prevent or modify some of the

* During the past few months we have been using smaller suppressive and smaller maintenance doses than we used previously; results have been generally quite satisfactory and will be reported elsewhere.

undesirable effects[42,45,94]. These include limitation of sodium chloride intake to 1 g or less, and, if necessary, the oral use of a diuretic such as potassium nitrate, to control retention of fluid; oral use of potassium chloride if necessary to control. deficits of potassium and chloride; personality appraisals and the avoidance or cautious use of the hormones in patients with prepsychotic tendencies[81]; early reduction of the initial suppressive doses to lower "maintenance doses" in all cases in which use of the hormones is prolonged[7, 28,45]; and use of estrogen (such as 5 mg of estrone twice weekly) in menopausal women somewhat intolerant to cortisone[42].

The incidence of troublesome side effects has been fairly low among patients given the hormones for a few days or weeks. As a result of the procedures just mentioned and others, the incidence of side effects has been declining among patients given the hormones for many weeks or months.

Potentiation of cortisone and *ACTH.* Attempts have been made to find some synergistic material which, when given with cortisone or ACTH, would enhance the effect of doses of cortisone or ACTH which were too small to produce side effects. Salicylates and vitamin C, and more recently insulin, have been recommended. So far we have seen no potentiation of cortisone from-such measures. The effects of cortisone or ACTH given in conjunction with gold salts to patients with rheumatoid arthritis are being investigated; detailed results have not been reported.

Gaps in Our Current Knowledge of Basic Facts. A completely rational and physiologic method for the administration of these hormones cannot yet be developed because we presently lack sufficient knowledge concerning certain basic facts. The main defects in our knowledge can be summarized briefly: (1) It is not yet known how much cortisone or ACTH is produced daily by the adrenal and pituitary glands of normal persons, or by patients with rheumatoid arthritis or with one of the other diseases influenced by these hormones. (2) Exogenous ACTH stimulates responsive adrenals to increase their production of endogenous cortisone but we do not know how much that increase is in any given case. (3) The administration of exogenous cortisone exerts a suppressive effect on the production of endogenous cortisone but we cannot yet measure, with any degree of precision, the decrease in production, which incidentally may vary considerably during the administration of. the exogenous cortisone. (4) We do not yet know whether cortisone (or compound F, hydrocortisone) is the only adrenal cortical hor-

mone[5,66,73]. Little is known about the metabolism of cortisone, about how much is utilized normally by the cells of the body, or how much is (normally) altered or destroyed in the body or excreted before it has had an effect.

Until we acquire some of this knowledge we can only attempt to develop, with intelligence and with concern for calculated risks, an empiric and reasonably safe method of administration.

Optimal Method of Administration of Cortisone and ACTH. For the investigative management of rheumatoid arthritis and other chronic conditions which seem now to require prolonged use of the hormones, the basic policy must be to provide the greatest symptomatic relief that is possible consistent with the avoidance of undesirable physiologic effects. If doses which are needed for full symptomatic relief produce significant side effects, one should reduce the dose and be content with less than full suppression of rheumatic symptoms, at least until a superior plan of administration is developed.

The optimal dosage and method of administration remain to be determined. Various plans of administration of cortisone and ACTH are under investigation[7,28,45,82]. The advantages and disadvantages of each plan have been described. The main schemes include (1) repeated, fairly short, interrupted courses using the same hormone for each course; (2) repeated, fairly short, interrupted courses, alternating the hormones; using for example cortisone for the first course, ACTH for the second course, cortisone for the third, and so forth; (3) more or less continued administration of either hormone: first the use of suppressive doses, then a gradual reduction to the level of an effective maintenance dose, and then the prolonged use of maintenance doses given either three days each week (intramuscularly) or daily (orally or intramuscularly). A significant number of rheumatoid patients are being satisfactorily managed by this latter method. The combined tie of cortisone and ACTH, given in differing proportions and by differing schedules, is also under investigation.

Oral Administration of Cortisone. The former remarks about cortisone refer chiefly to its intramuscular administration. Current investigations indicate that cortisone is also effective when given orally in tablet form. In May, 1949, one of our rheumatoid patients responded very well to the oral administration of capsules of highly concentrated adrenal cortex extract (Upjohn) containing compounds E and F[42,76]. From this experience and from the observa-

tions of Heilman and Kendall[37] who administered cortisone to animals we concluded that the oral use of cortisone would be effective. Satisfactory results from cortisone tablets given to rheumatoid patients have been reported by Freyberg and his associates[29], by Kuzell and Schaffarzick[60], and by Boland and Headley. Our own results have also been satisfactory[39f,43,45]; details regarding 100 cases will be reported soon with my colleagues, Ward, Slocumb, Polley, and Lowman[107]. The total daily oral dose which is effective in most cases approximates in amount the effective daily intramuscular dose. It is the preliminary impression of Freyberg and his associates, of Boland and Headley, and of ourselves that when small doses are given orally several times a day the clinical effect may be more satisfactory and the incidence of undesired effects may be lower than when one large daily dose is given intramuscularly. The new method may be more physiologic, approximating the more or less continuous output of small amounts of cortisone-like material from the human adrenal cortex.

Extension of the Use of these Hormones against Other Conditions. When the effectiveness of cortisone and ACTH against rheumatoid arthritis became apparent we remembered that the ameliorating effect of jaundice and pregnancy is not disease specific but group specific[39k,m]. We remembered also that jaundice and pregnancy appear to exert an anti-allergic, as well as an anti-rheumatic, effect[39k]. Therefore it seemed logical to hope that these hormones would be found to be useful against certain non-rheumatic as well as other rheumatic diseases. If one could assume that cortisone (or a cortisone-like substance such as Kendall's compound F) is the ameliorating agent operating in jaundice or pregnancy, cortisone and ACTH might be expected to be effective against (1) various diseases commonly relieved by jaundice or pregnancy[39m]; (2) diseases which involved essentially the same histologic types of tissues (muscular, fibrous, collagenous) which are affected in rheumatoid arthritis; and (3) certain allergic conditions[39k].

For these reasons, therefore, the first extension of the use of these hormones by us, and then by others, was to cases of lupus erythematosus disseminatus, and acute rheumatic fever, then to various allergic conditions.

Results in rheumatic fever. Following the use of either hormone, the acute manifestations of rheumatic fever have generally subsided quickly, some of them (fever, polyarthritis, tachycardia, "toxemia") usually within a few days, others usually within two to three weeks (increased sedimentation rates, aug-

mented P-R intervals, hyperglobulinemia)[2,41,42,44-46,68,69,101,102]. When present, pre-existing chronic valvular damage and old cardiac hypertrophy have remained unchanged. But in some cases certain manifestations of acute carditis have been promptly lessened or abolished, and within the limits of our short follow-up studies (average: a few months) no definite persisting signs of new or increased old carditis have developed from the acute attacks which were suppressed by the hormones.

In a few reported cases in which there was frank or impending cardiac decompensation, use of the hormones has caused troublesome but generally transient retention of fluid. But in most patients with acute rheumatic fever and acute carditis few if any major side effects have developed.

Cortisone and ACTH, although they suppress symptoms, do not "cure" rheumatic fever, nor is it yet certain that they shorten the inherent duration of its acute phase. Hence they must be given until the natural duration of the acute phase, generally six to twelve weeks, has run its course. Otherwise, as pointed out by my colleagues, Drs. A. R. Barnes and H. L. Smith, some or all of the acute manifestations will reappear and remain either until the hormone is given again or until the acute phase has spent itself.

Some evidence suggests that the proliferative as well as the exudative manifestations of acute rheumatic carditis may be suppressed by these hormones. If so, their proper use may prevent much pathologic change in the heart. But prolonged observations will be required to determine whether or to what extent these hormones will prevent the initial development or aggravation of rheumatic carditis.

Results in other conditions. The acute articular manifestations of gout[31,38,65,69,80,91,101,102,111,112] and the articular complications of disseminated lupus erythematosus[11,40,42,69,87,101,112], ulcerative colitis[20,23,42,58,112], psoriasis[69,77,102] and tuberculosis[42] have been found to be-responsive to these hormones in most, but not in all cases. Symptoms of osteo-arthritis have been modified in some cases, but not in others.

The hormonal effects on the non-articular features of these diseases have been varied. Many features of disseminated lupus erythematosus have been temporarily suppressed, others have not. Although remissions, not cures, have been induced, use of the hormones has apparently been a life-saving measure in certain acute crises of this disease. In ulcerative colitis, symptomatic relief of intestinal symptoms has been provided more often than objective improvement. In psoriasis, articular lesions have been more responsive

than the lesions of skin. In tuberculosis, cortisone and ACTH appear to control hyperergic tissue reactions, and may reduce certain symptoms[27,42,103]. But the hormones exert no bactericidal or bacteriostatic effect, and because they inhibit formation of fibroblasts it has been suggested that they may foster the spread of active tuberculous lesions[27,34,42,63,90,103]. Therefore they should be used with considerable caution in tuberculous infections, at least for the present. But cortisone does not produce lysis of already existing granulation tissue.

Several types of allergic reactions have been suppressed during the use of these hormones and sometimes for varying lengths of time thereafter: ragweed hay fever[15,42], bronchial asthma[13,15,102], status asthmaticus[102], infantile atopic eczema, urticaria, and certain skin and other reactions due to penicillin, gold, and other drugs[13].

One of the more promising fields of usefulness for these hormones appears to be the acute and subacute inflammatory diseases of the eye: uveitis, scleritis, iridocyclitis, keratitis, chorioretinitis, sympathetic ophthalmia, and vernal conjunctivitis[35,47,59,96,102]. In some cases cortisone in eye drops or ophthalmic ointment has been effective; in other cases subconjunctival or intragluteal injections were employed.

Less striking but still of considerable interest have been the results in some cases of cranial arteritis[85], periarteritis nodosa[85], dermatomyositis[69,102], nephrosis[25,55,63], sprue, burns[19,110], and certain blood dyscrasias[22,97], especially leukemia and acquired hemolytic anemia.

The possible influence of these hormones on many other conditions is being investigated, and optimistic preliminary reports concerning some of them have appeared[14,72,102]. But it will take years to evaluate the results critically. If one confines his attention to those diseases about which opinion seems to be fairly unanimous after one or two years of experience, one finds that about fifteen or twenty diseases can be modified markedly or suppressed almost completely, at least temporarily. What makes this the more interesting is that most of these responsive diseases have been heretofore peculiarly resistant to control or even to temporary modification by any previous remedy.

Speculations on the Mode of Action. Many of the numerous physiologic effects of cortisone and ACTH appear to be non-specific, meaning that if large enough doses are given long enough these effects will develop in anyone, normal or diseased. But the ability of these hormones to ameliorate markedly

almost the whole symptom complex of certain diseases appears to be group specific; at least the outstanding clinical results occur in the rheumatic, allergic, and collagen diseases[39n].

But how these hormones accomplish, for example, their antirheumatic effect is still quite unknown[39n,0,45]. Because rheumatoid arthritis infrequently complicates Addison's disease and because the daily dose required to suppress the responsive inflammation is considerably greater than that required by addisonian patients, it appears that the hormones do not merely correct some simple deficiency, such as one from an inadequate production of cortisone or ACTH. The administration of cortisone may correct a relative, not an absolute, deficiency and satisfy an increased tissue requirement for the hormone[45]. Thus current opinion is that the hormones act at the tissue, or cell, level. But this tentative conclusion must be the subject of much further study.

In providing relief, these hormones do not kill germs or appear to remove the unknown etiologic irritants of the conditions which they ameliorate. Thus they do not "cure" the diseases the symptoms of which they modify so profoundly. But in an unknown manner they provide the susceptible tissues with a shield-like buffer or protection against a wide variety of irritants.

The hormones influence beneficially, not the irreversible pathologic anatomy or ashes of disease, but the reversible part of the responsive diseases, their pathologic physiology, that is, the reaction of tissues to the irritant.

To use a figure of speech, these hormones appear not to extinguish the fire nor to act like a carpenter to repair the fire's damage. Instead they appear to "dampen the fire" or to provide, as it were, an asbestos suit behind which the patient, like some biblical Shadrach, Meshach, or Abednego, protects his tissues from the fire. If this protection is removed prematurely before the fire has spent itself, the patient and his tissues will react again to the burning. But if the protection is not discarded until the natural duration of the fire is over, the patient remains largely free of symptoms and apparently "well".

Search for Substitutes for Cortisone and ACTH. Miscellaneous Steroids. - Because of the cost, limited supplies and potential side effects of cortisone and ACTH, some effective steroidal substitute has been intensively sought. So far the search has been fruitless. About 50 steroids have been tested by us and others for antirheumatic and other properties[14,18,30,61,74,76]. With the exception of 17-hydroxycorticosterone (Kendall's compound F, substance M of Reichstein) none has given significant results in the limited range of doses which has thus far been explored. But a comparative study, by Polley and

Mason, of the chemical configurations of these ineffective steroids with those of the potent compounds E and F, has revealed the structural requirements which appear to give the steroid nucleus its antirheumatic properties and which appear to be responsible for the physiologic activity of cortisone. They are a ketone group at carbon-j, either a ketone or a hydroxyl group at carbon-II, a ketone group at carbon-20, a hydroxyl group at carbon-17 and at carbon-21, and a double bond between carbon atoms 4 and 5.

Compound F (Kendall) - Certain data suggest that Kendall's compound F (17-hydroxycorticosterone:hydrocortisone) may be the ultimate product of the adrenal cortex[66,73]. Although our supplies of compound F have been very meagre, the antirheumatic activity of this compound appears to be comparable to that of cortisone[43,45,76].

Summary of Present Status. Depending on the amount of their experience with these hormones and also upon their own aggressiveness or conservatism, American physicians, including clinical investigators, would express widely differing opinions as to the present status of these hormones in general medicine. Until recently, the hormones were used at the Mayo Clinic, not particularly as forms of treatment, but as tools for physiologic investigations. But physicians cannot remain academic and aloof to the army of patients who ask, "How soon can you treat me with these substances safely and within my means?"

Many investigators with one or two years of experience in the use of these hormones believe that cortisone and ACTH can now be given limited practical application in the management of conditions which may require relatively short-term usage for a few days or weeks, for example, acute gouty arthritis, acute rheumatic fever, acute ocular inflammations, acute or seasonal allergies, acute skin sensitivities, and acute crises of disseminated lupus erythematosus.

As for the application of cortisone and ACTH to the management of responsive chronic diseases, the many investigations now being made are revealing the scope and limits of their usefulness. Certain conservative, critical rheumatologists have already expressed their belief that the careful use of these hormones as therapeutic agents for rheumatoid arthritis is justified and appears properly to be impending.

To permit the appropriate therapeutic and investigative use of these hormones, the United States Food and Drug Administration has released them for sale to all licensed American physicians.

Requirements for the Orderly Development of Cortisone and ACTH as Therapeutic Agents

For the proper and orderly development of cortisone (or the cortisone-like compound F) and ACTH as therapeutic agents, chemists must learn how to make these materials in more or less unlimited quantities, and physiologists and physicians must try to learn how they produce their beneficial effects, or in lieu of such basic knowledge, physicians must learn how to use them empirically but nevertheless intelligently and safely. As stated elsewhere, "In the presence of functioning adrenal glands we must learn how to co-operate with them rather than to try to dominate them or take over their functions"[43].

Problems of production. In the competition for the attainment of their respective goals the biochemist and chemical manufacturer are somewhat ahead of the physiologist and the clinical investigator. Despite enormous difficulties, the production of these hormones, especially cortisone, has been greatly increased.

Cortisone. - Although none of the thirty-six steps required to convert desoxycholic acid into cortisone has been by-passed, some of the steps have been made less costly, less time-consuming, and productive of greater yields; hence the cost has fallen from an estimated production cost of $1,000 a gram in 1948 to the current (November, 1950) sales price of $35.00 per gram. Despite certain news reports, no cortisone has yet been made from *Strophanthus* plants[12,104], soybeans, or Mexican yams. But the search for new starting materials for the partial synthesis of cortisone, and for methods for its total synthesis, continues and will doubtless be successful in time.

ACTH. - The pituitary glands of animals (beef, horses) other than the pig now yield significant amounts of potent adrenocorticotropic hormone (Armour's ACTH; Wilson's corticotropin). Potent ACTH is also being made from the pituitaries of whales by Scandinavian scientist@.

A "long-acting" preparation of ACTH, prepared by Armour & Co., has given satisfactory results in a few cases of rheumatoid, gouty and psoriatic arthritis, rheumatic fever, and ulcerative colitis. Maximal duration of activity was forty-eight hours[112].

Several investigators[1,62,64,71] have suggested that peptide fragments of ACTH may retain physiologic activity, possess a much smaller molecular weight than the parent product and provide the hope that eventual synthesis of a potent ACTH peptide may be accomplished.

Compound F (Kendall).- Until recently, compound F of Kendall (substance M of Reichstein) was obtained only by extraction from adrenal glands. But now the biologic conversion or biosynthesis of compound F from substance S (Reichstein) is being accomplished[33,36,70] as also is the synthetic production of compound F from a precursor of compound E[109].

Development of a rational (physiologic) method of administration. As stated above, the development of a rational or physiologic method for the administration of these hormones will not be fully accomplished until more has been learned about the physiology of the pituitary and adrenal glands in the diseases which respond to these hormones, and about the metabolism of cortisone, hydrocortisone (compound F of Kendall) and ACTH, in health and in disease.

One of the prime requirements is the development ofsatisfactory biologic or biochemical methods for estimating the amount of these substances in bodily fluids and tissues. Thus we could learn how much of them are produced by the pituitary and adrenals of normal persons, or of patients with rheumatoid arthritis or other diseases. The present chromatographic methods are useful, but simpler, more refined methods are desired[113].

Much more must be learned about the function of the pituitary and adrenal glands in rheumatic and other patients as compared to normal persons. The majority of investigative rheumatologists and endocrinologist are assuming that the pituitary and adrenal glands are functioning normally in most rheumatoid patients, the conclusion being based chiefly on eosinophilic responses to a single injection of exogenous ACTH (Thorn test)[101], and on studies of urinary steroids. But the fact that the adrenals of most rheumatoids apparently secrete normal amounts of their eosinopenic-producing hormone (cortisone?) under stimulation by exogenous ACTH does not necessarily prove indisputably that the pituitary of the rheumatoid is producing normal amounts of endogenous ACTH, or that the adrenals of the rheumatoid are, without such added stimulation, producing normal amounts of cortisone or cortisone-like material. And of course what are normal and adequate amounts for a healthy person may not constitute adequate amounts for the ill.

Despite the fact that studies of the histologic structure of glandular tissues do not always permit one to form precise opinions as to their physiologic potency or normalcy, a more comprehensive study of the histology of the pituitary and adrenal glands of rheumatoid patients (also of others who

respond to these hormones), and "normal" persons, for example, persons killed in accidents, and so forth, must be made at necropsy. Are the pituitary and adrenal glands of rheumatoid normal histologically, or are there some (primary or secondary) evidences of disease therein? A British investigator[75] has recently recorded his belief that there may be a characteristic histologic abnormality in the pituitary of rheumatoid arthritics, an abnormality not found in controls. Others have recently reported the presence, in rheumatoid patients, of certain abnormalities in the metabolism of steroids which may indicate a faulty secretion or an abnormal metabolism of the adrenocortical hormones in this disease[21,88]. If true, the significance of these abnormalities remains to be determined.

From studies made with cortisone or ACTH labelled with radioactive isotopes much could be learned about the metabolism of these hormones. ACTH tagged with radioiodine and injected into the heart of animals passes at once into the adrenal cortex where the radioactivity remains for about two hours in rapidly decreasing amounts[8,9]. Studies with cortisone labelled with tritium, a radio-isotope of hydrogen, are also being made[16]. By these and other methods it may someday be possible to determine whether there is, at the tissue level, a decreased utilization or an increased requirement for cortisone.

Characteristics of substance X. Until some of the above-mentioned investigative methods have been developed we cannot test adequately the hypothesis that the effective substance X of jaundice and that of pregnancy are identical and that either or both are cortisone (or compound F). Cortisone or compound F is presently the most likely candidate for substance X. The characteristics of substance X are: (1) that it is antirheumatic and antiallergic, that, in other words, it is group specific rather than disease specific; (2) that it develops rapidly in jaundiced patients, more slowly in pregnant patients, and appears to operate in these patients during a characteristic period of time; and (3) that its clinical effects are accomplished rapidly and are more or less complete but are transient. Cortisone appears to possess most of these characteristics. But in the light of our newer knowledge we must study the pituitary-adrenal relationships during the changing phases of (natural and experimental) jaundice and of pregnancy in rheumatic and non-rheumatic patients. Similar studies should also be made in rheumatoid patients receiving gold salts. Thus we may learn how pregnancy and jaundice (and much less commonly, gold salts) provide their benefits. We must test rigidly the valid-

ity of the interesting but unproved assumptions that in pregnancy the production of cortisone may be markedly increased[105] and that in hepatitis with jaundice the normal (?) process of inactivation or destruction of cortisone, perhaps by the liver, may be lessened with a resultant relative increase in cortisone[45]. (No evidence of increased adrenal activity, as revealed by studies of urinary steroids, was found by Sprague, Mason, and Power among seven men and nine women with jaundice due to obstruction, cirrhosis, or viral hepatitis.)

Empiric Use of Cortisone and ACTH

Clinical investigators, while waiting for the collection of these missing data, and for the development of these needed methods, can do much to insure the reasonably intelligent and safe, even though empiric, use of these hormones. Long-term studies of various plans of administration may show how to provide the greatest relief with the least risk, and may even show how to project the hormonal effects farther into the posthormonal period than seems possible now. Clinical and metabolic studies of the effect of repeated small doses of cortisone or hydrocortisone given orally may also constitute another step in the direction of developing the most physiologic method of administration.

During the past year I have often been asked, "Do you think we shall be able to use these or similarly effective substances with safety, or to reproduce continuously the benefits of pregnancy or jaundice?" I believe that we shall. The pregnant woman develops a strikingly altered and improved physiologic state which is generally antagonistic to the continuation of the symptoms of rheumatoid arthritis. She normally tolerates this altered, antirheumatic state for months without any disturbing evidences of hormonal imbalance (unless her white striae are somewhat analogous to the red striae of hypercortisonism). Indeed she often feels "better than I have for years". As we learn of the agent and mechanism responsible for her antirheumatic state, so we may learn to reproduce that basic mechanism for the physiologic good of others.

Conclusion

Cortisone and ACTH today represent unframed pictures. No boundaries can yet be established to define either their full potentialities or their limitations.

These hormones still belong to the physiologist and to the clinical investigator as much as, if not more than, to the practicing physician. But as Professor Starling said many years ago, "The physiology of today is the medicine of tomorrow" [95].

But whatever the immediate or future destiny of these hormones may be, in the field of practical therapeutics they already have demonstrated clearly the potential reversibility of many disease processes which have been thought heretofore to be more or less relentlessly progressive. Thus they have given a sound basis for much hope. In particular, they constitute powerful tools with which we can investigate many problems related to the etiology and treatment of a wide variety of diseases.

1. E. B. Astwood, A. P. Cleroux, R. W. Payne, and M. S. Raben, Therapeutic studies on some newer corticotropbic (ACTH) preparations, *Bull. New Engl. Med. Center,* 12 (1950) 2-10.
2. A. R. Barnes, Effects of cortisone and ACTH in 14 patients with acute rheumatic fever, *Proc. Staff Meetings Mayo Clinic, 25* (1950) 478-479.
3. W. Bauer, J. E. Giansiracusa, and M. W. Ropes, The natural course of rheumatoid arthritis and the changes induced by ACTH, *Trans. Assoc. Am. Physicians, 63* (1950) 76-78.
4. W. Bauer, E. W. Boland, R. H. Freyberg, W. P. Holbrook, and E. F. Rosenberg, *Discussions Seventh International Congress on Rheumatic Diseases, New York,* May 30-June 3, 1949.
5. E. W. Boland, The effects of cortisone and adrenocorticotropic hormone (ACTH) on certain rheumatic diseases, *California Med., 72* (1950) 405-414.
6. E. W. Boland and N. E. Headley, Effects of cortisone acetate on rheumatoid arthritis, *J. Am. Med. Assoc.,* 141 (1949) 301-308.
7. E. W. Boland and N. E. Headley, Management of rheumatoid arthritis with smaller (maintenance) doses of cortisone acetate, *J. Am. Med. Assoc,* 144 (1950) 365-372.
8. K. Brøchner-Mortensen, J. Georg, C. Hamburger, E. Snorrason, M. Sprechler, A. Videbaek, and O. T. K. With, Hormonbehandling af polyarthritis chronica, *Ugeskrift Laeger,* 112 (1949) 1255-1277.
9. E. C. Brodie, E. B. Wallraff, A. L. Borden, W. P. Holbrook, C. A. L. Stephens Jr., D. F. Hill L. J. Kent, and A. R. Kemmerer, Urinary excretion of certain amino acids during ACTH and cortisone treatment of rheumatoid arthritis, *Proc. Soc. Exptl. Biol. Med., 75* (1950) 285-287.
10. J. S. L. Browne, Corticosterone and "*Cortin*" *in* human urine, *Josiah Macy, Jr. Foundation Conference on Bone and Wound Healing. Second Meeting,* Josiah Macy, Jr. Foundation, New York, 1942, pp. *43-47.*

11. L. A. Brunsting, C. H. Slocumb, and J. W. Didcoct, Effects of cortisone on acute disseminated lupus erythematosus, *Arch. Dermatol. and Syphilol.,* 63 (1951) 29-48.
12. R. K. Callow, Expedition to Nigeria. M. R. C. search for tropical plants, *Brit. Med. J.,* 1 (1950) 1484-1485.
13. R. A. Carey, A. McG. Harvey, J. E. Howard, and P. F. Wagley, The effect of adrenocorticotropic hormone (ACTH) and cortisone on drug hypersensitivity reactions, *Bull. Johns Hopkins Hosp.,* 87 (1950) 354-386.
14. J. M. Carlisle, Cortisone (compound E): S*ummary* of its clinical uses, *Brit. Med. .J.,* 2 (1950) 590-595
15. H. M. Carryer, G. A. Koelsche, L. E. Prickman, C. K. Maytum, C. F. Lake, and H. L. Williams, Effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen, *J; Allergy,* 21 (1950) 282-287.
16. Chemical and Engineering Reports 118th National Meeting of the ACS: Cortisone Chemistry, *Chem. Eng. News,* 28 (1950) 3306.
17. W. S. C. Copeman, O. Savage, P. M. F. Bishop, E. C.Bodds, B. Gottlieb, J. H. H. Glyn, A. A. Henly, and A. E. Kellie, A study of cortisone and other steroids in rheumatoid arthritis, *Brit. Med. J.,* 2 (1950) 849-855.
18. W. S. C. Copeman, J. J. R. Duthie, E. Fletcher, G. N. Myers, O. Savage, F. D. Hart, J. H. Kellgren, P. Lehman, G. D. Kersley, H. A. Burt, E. G. L. Bywaters, and S. J. Hart&all, Treatment of rheumatoid arthritis with deoxycortone and ascorbic acid, *Brit. Med. J.,* 1 (1950) 1006-1007.
19. P. O. Crassweller, A. W. Farmer, W. R. Franks, and A. D. McLachhn, Three cases of severe bum treated with cortisone, *Brit. Med. J.,* 2 (1950) 977-981.
20. W. H. Dearing and P. W. Brown, Experiences with cortisone and ACTH in chronic ulcerative colitis, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 486-488.
21. K. Dobriner, S. Lieberman, H. Wilson, M. Dunham, I. F. Sommerville, and C. P. Rhoads, Adrenal function and steroid excretion in disease; in J. R. Mote: *Proceedings of the Second Clinical ACTH Conference, Philadelphia,* The Blakiston Co., 1951, Vol. I, pp. 65-75.
22. J. J. R. Duthie, Clinical trials of ACTH; preliminary report, *Edinburgh Med. J.,* 57 (1950) 341-364.
23. C. H. DuToit and W. Bauer, The effect of ACTH in ulcerative colitis; in J. R. Mote, *Proceedings of the First Clinical ACTH* Conference, *Philadelphia,* The Blakiston Co., 1950, pp. 459-468.
24. G. Edström, Undersökningar över vissa hormoneffekter vid kronisk artrit; (ACTH, hypofysinplantation, via adrenalinretning, DOCA, progestin, testosteron, *Svenska Läkartidn.,* 46 (1949) 2697-2713.
25. E. B. Farnsworth, Metabolic changes associatedwith administrationof adrenocorticotropin in the nephrotic syndrom, *Proc. Soc. Exptl. Biol. Med.,* 74 (1950) 60-62.
26. A. P. Forbes, Effect of operations on the 17-ketosteroid excretion in man, *Josiah Macy, Jr. Foundation Conference on Bone and Wound Healing, Third Meeting, New York,* Josiah Macy, Jr. Foundation, 1943, pp. 146-167.
27. S. Freeman, J. Fershing, C. C. Wang, and L. C. Smith, The effect of ACTH on patients with pulmonary tuberculosis; in J. R. Mote, *Proceedings of the First Clinical ACTH Conference, Philadelphia,* The Blakiston Co., 1950, pp. 508-521.

28. R. H. Freyberg, Effects of cortisone and ACTH in rheumatoid arthritis, *Bull. N. Y. Acad. Med.,* 26 (1950) 206-211.
29. R. H. Freyberg, C. T. Traeger, C. H. Adams, T. Kusco, H. Wainerdi, and I. Bonomo, Effectiveness of cortisone administered orally, *Science,* 112 (1950) 429.
30. C. M. Guest, W. H. Kammerer, R. L. Cecil, and S. A. Berson, Epinephrine, pregnenolone, and testosterone in the treatment of rheumatoid arthritis, *J. Am. Med. Assoc.,* 143 (1950) 338-344.
31. A. B. Gutman and T. F. Yü, Effects of adrenocorticotropic hormone (ACTH) in Gout, *Am. J. Med.,* 9 (1950) 24-30.
32. D. V. Habif, C. C. Hare, and G. H. Glaser, Perforated duodenal ulcer associated with pituitary adrenocorticotropic hormone (ACTH) therapy, *J. Am. Med. Assoc.,* 144 (1950) 996.
33. W. J. Haines, *Recent Progress in Hormone Research,* Vol. 7, Academic Press, New York 1952.
34. P. D'A. Hart and R. J. W. Rees, Enhancing effect of cortisone on tuberculosis in the mouse, *Lancet, 2* (1950) 391-395.
35. A. M. Harvey, J. E. Howard, and A. A. Kattus, The effect of adrenocorticotropic hormone (ACTH) and cortisone on certain diseases of the eye in which hypersensitivity plays a role, *Bull. Johns Hopkins Hosp.,* 87 (1950) 461-481.
36. O. Hechter, R. P. Jacobsen, R. Jeanloz, H. Levy, C. W. Marshall, G. Pincus, and V. Schenker, The bio-oxygenation of steroids at C-II, *Arch. Biochem.,* 25 (1950) 457-460.
37. F. R. Heilman and E. C. Kendall, The influence of II-dehydro-17-hydroxycorticosterone (compound E) on the growth of a malignant tumor in the mouse, *Endocrinology,* 34 (1944) 416-420.
38. L. Hellman, Production of acute gouty arthritis by adrenocorticotropin, *Science,* 109(1949)280-281.
39. P. S. Hench, *(a)* Chronic infectious arthritis, *Mayo Clinic Bull.,* 6 (1924) 1; *(b)* The protean manifestations of chronic infectious arthritis (with a note on treatment), *Med. Clin. N. Am.,* 8 (1925) 1295-1306; (c) The systemic nature of chronic infectious arthritis, *Atlantic Med. J.,* 28 (1925) 425-436; *(d)* Analgesia accompanying hepatitis and jaundice in cases of chronic arthritis, fibrositis, and sciatic pain, *Proc. Staff Meetings Mayo Clinic,* 8 (1933) 430-436; *(e)* The analgesic effect ofhepatitis and jaundice in chronic arthritis, fibrositis, and sciatic pain, *Ann. Internal Med.,* 7(1934) 1278-1294; *(f)* A clinic on some diseases-of joints. IV. The inactivation of chronic infectious arthritis and fibrositis by jaundice, *Med. Clin. N. Am.,* 19 (1935) 573-583; *(g)* Effect of jaundice on chronic infectious arthritis and on primary fibrositis, *J. Am. Med. Assoc.,* 109(1937) 1481-1484; *(k)* Effect of jaundice on chronic infectious (atrophic) arthritis and on primary fibrositis. Further observations. Attempts to reproduce the phenomenon, *Arch. Internal Med.,* 61(1938) 451-480; 495-500; *(i)* The ameliorating effect of pregnancy on chronic atrophic (infectious, rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis, *Proc. Staff Meetings Mayo Clinic,* 13 (1938) 161-167; *(j)* Effect of spontaneous jaundice on rheumatoid (atrophic) arthritis. Attempts to reproduce the phenomenon, *Brit. Med. J., 2* (1938) 394-398; *(k)* The advantages of hepatic

injury and jaundice in certain conditions, notably the rheumatic diseases, *Med. Clin.* N. *Am.,* 24(1949)1209-1237;*(l)* Personal communication to Dr. Augustus D. Gibson, Merck & Co., Inc., Sept. 4, 1948; *(m)* The potential reversibility of rheumatoid arthritis, *Proc. Staff Meetings Mayo Clinic,* 24 (1949) 167-178; *Ann. Rheumatic Disease, 8* (1949) 90-96; (n) Cortisone and ACTH in clinical medicine, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 474-476; *(o)* The present status of cortisone and ACTH in general medicine, *Proc. Roy. Soc Med.,43* (1950) 769-773 ; *(p)* (Chairman) Discussion, *Ann. Rheumatic Diseases, 9* (1950) 397.

40. P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, The effect of a hormone of the adrenal cortex (17-hydroxy-II-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. (Preliminary Report.) *Proc. Staff Meetings Mayo Clinic, 24* (1949) 181-197; *Ann. Rheumatic Diseases,* 8 (1949) 97-104.
41. P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, The effect of a hormone of the adrenal cortex, cortisone (17-hydroxy-II-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis and acute rheumatic fever, *Trans. Assoc. Am. Physicians,* 62 (1949) 64-80.
42. P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever, and certain other conditions, *Arch. Internal Med.,* 85 (1950) 545-666.
43. P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, The antirheumatic effects of cortisone and pituitary ACTH, *Trans. Studies Coll. Physicians Phila.,* 18 (1950) 95-172.
44. P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, The effects of the adrenal cortical hormone (17-hydroxy-II-dehydrocorticosterone: cortisone) and of pituitary adrenocorticotropic hormone (ACTH) on rheumatoid arthritis and rheumatic fever, *Proc. Seventh Intern. Congr. Rheumatic Diseases, New York,* May 30-June 3, 1949. W. B. Saunders Co., Philadelphia. (In the press.)
45. P. S. Hench, C. H. Slocumb, H. F. Polley, and E. C. Kendall, Effect of cortisone and pituitary adrenocorticotropic hormone (ACTH) on rheumatic diseases, *J. Am. Med. Assoc.,* 144 (1950) 1327-1335.
46. P. S. Hench, C. H. Slocumb, A. R. Barnes, H. L. Smith, H. F. Polley, and E. C. Kendall, The effects of the adrenal cortical hormone. 17-hydroxy-II-dehydrocorticosterone (compound E) on the acute phase of rheumatic fevers. (Prelim. Rept.), *Proc. Staff Meetings Mayo Clinic,* 24 (1949) 277-297.
47. J. W. Henderson and R. W. Hollenhorst, Effects of cortisone on certain ophthalmic diseases, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 490-491.
48. H. Hennings, The whale hypophysis with special reference to its ACTH content (Prelim. Rept.), *Acta Endocrinol.,* 5 (1950) 376-386.
49. P. F. A. Hoefer and G. H. Glaser, Effects of pituitary adrenocorticotropic hormone (ACTH) therapy. Electroencephalographic and neuropsychiatric changes in fifteen patients, *J. Am. Med. Assoc.,* 143 (1950) 620-624.
50. W. P. Holbrook, D. F. Hill, C. A. L. Stephens Jr., and L. J. Kent, Effects of ACTH and cortisone on rheumatoid arthritis, *Arizona Med.,* 7 (1950) 43-44.

51. D. J. Ingle, Diabetogenic effect of some cortin-like compounds, *Proc. Soc. Exptl. Biol. Med.,* 44 (1940) 176-177.
52. E. Jonsson, Endokrinologi och reumatologi, *Nord. Med.,* 44 (1950) 1891-1895.
53. E. Jonsson, K. Berglund, E. Y. Htianson, N. G. Hävermark, and H. Laurell, Biochemical and clinical studies in rheumatoid arthritis during administration of adrenocorticotropic hormone (ACTH). (Prelim. Rept.), *Acta Endocrinol., 4* (1950) 229-239.
54. E. Jonsson, K. Berglund, N. G. Hävermark, G. Nyström, and F. Paulsen, Endokrinologiska synpunkter p9 vissa reumatiska och andra mesenkymala sjukdomstills&nd, *Svenska Läkartidn.,* 46 (1949) 1921-1931.
55. N. M. Keith, M. H. Power, and G. W. Daugherty, The action of cortisone in nephritis *with* edema, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 491-492.
56. E. C. Kendall, Some observations on the hormone of the adrenal cortex designated compound E, *Proc. Staff Meetings Mayo* Clinic, 24 (1949) 298-301.
57. E. C. Kendall, Cortisone, *Ann. Internal Med.,* 33 (1950) 787-796.
58. J. B. Kirsner, W. L. Palmer, and A. P. Klotz, ACTH and cortisone in chronic ulcerative colitis: a comparison ofclinical effects, *J. L.ab. Clin. Med.,* 36 (1950) 846.
59. R. Koff, S. Rome, R. Kasper, R. R. Commons, R. Button, and P. Starr, Subconjunctival injection of cortisone in iritis, *J. Am. Med. Assoc.,* 144 (1950) 1259-1260.
60. W. C. Kuzell and R. W. Schaffarzick, Oral administration of cortisone acetate, *Stanford Med. Bull.,* 8 (1950) 212-213.
61. E. Lewin and E. Wassén Effect of combined injections of deoxycortone acetate and ascorbic acid on rheumatoid arthritis, *Lancet,* 2 (1949) 993.
62. C. H. Li, Recent advances in anterior pituitary hormones (with special reference to adrenocorticotropic hormone ACTH), *Ned. Tijdschr. Geneesk.,* 94 (1950) 1193-1196.
63. J. A. Luetscher Jr., Q. B. Deming, J. Harvey, W. Lew, and L. J. Poo, Treatment of nepkosis with cortisone, *J. Clin. Invest.,* 29 (1950) 1576-1587.
64. R. Luft, B. Sjogren, and C. H. Li, Results of administration of adrenocorticotropically active peptides (ACTH peptides) to a patient suffering from rheumatoid arthritis, *Acta Endocrinol.,* 3 (1949) 299-309.
65. H. M. Margolis and P. S. Caplan, Treatment of acute gouty arthritis with pituitary adrenocorticotropic hormone (ACTH), *J. Am. Med. Assoc.,* 142 (1950) 256 258.
66. H. L. Mason, Isolation of adrenal cortical hormones from urine: 17-hydroxycorticosterone and 17-hydroxy-II-dehydrocorticosterone, *J. Biol. Chem.,* 182 (1950) 131-149; also printed in *Pituitary-adrenal Function,* American Association for the Advancement of Science. (A booklet.)
67. H. L. Mason, W. M. Hoehn, and E. C. Kendall, Chemical studies of the suprarenal cortex. IV. Structures of compounds C, D, E, F, and G., *J. Biol. Chem.,* 124 (1938) 459474.
68. B. F. Massell, J. E. Warren, G. P. Sturgis, B. Hall, and E. Craige, The clinical response of rheumatic fever and acute carditis to ACTH, New *Engl. J. Med., 242* (1950) 641-47; 692-698.

69. C. McEwen and J. J. Bunim, Effects of cortisone and ACTH on various types of rheumatic diseases, *Trans. Assoc. Am. Physicians,* 63 (1950) 79-88.
70. D. A. McGinty, G. N. Smith, M. L. Wilson, and C. S. Worrel, The biosynthesis of 17-hydroxycorticosterone from 11-desoxy-17-hydroxycorticosterone, Science, 112 (1950) 506.
71. P. Morris and C. J. O. R. Morris, Isolation of a polypeptide with high adrenocorticotrophic activity, *Lancet,* 1(1950) 117-118.
72. J. R. Mote, The development of ACTH and the role of the adrenal gland in human disease, *World Med. Assoc. Bull.,* 2 (1950) 71-86.
73. D. H. Nelson, H. Reich, and L. T. Samuels, Isolation of a steroid hormone from the adrenal-vein blood of dogs, *Science,* III (1950) 578-579.
74. G. Nyström, Attempts to reproduce the effects of ACTH or of compound E in rheumatoid arthritis by means of other hormones and steroids, *Acta Endocrinol.,* 4 (1950) 240-244.
75. A. G. E. Pearse, The hypophysis in rheumatoid arthritis *Lancet,* I (1950) 954-955.
76. H. F. Polley and H. L. Mason, Rheumatoid arthritis. Effects of certain steroids other than cortisone and of some adrenal cortex extracts, *J. Am. Med. Assoc.,* 143 (1950) 1474-1481.
77. H. F. Polley, P. S. Hench, and L. A. Brunsting, Effects of cortisone and ACTH on psoriatic arthritis, *Proc. Central Soc. Clin. Res.,* 23 (1950) 81-82; (Abstr.) *J. Lab. Clin. Med.,* 36 (1950) 973-974.
78. C. Ragan, A. W. Grokoest, and R. H. Boots, Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis, *Am. J. Med.,* 7 (1949) 741-750.
79. T. Reichstein and C. W. Shoppee, The hormones of the adrenal cortex; in R. S. Harris and K. V. Thimann, *Vitamins and Hormones; Advances in Research and Applications,* Academic Press, Inc., New York, 1943, Vol. I, pp. 345-413.
80. W. D. Robinson, J. W. Corm, W. D. Block, and L. H. Louis, Role of the adrenal cortex in urate metabolism and in gout, *Proc. Central Soc. Clin. Res.,* 21 (1948) *23-24; J. Lab. Clin. Med.,* 33 (1948) I472-1473.
81. H. P. Rome and F. J. Braceland, Use of cortisone and ACTH in certain diseases: Psychiatric aspects, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 495-497.
82. E. F. Rosenberg, Experiences with compound E (cortisone), other adrenal cortical steroids, and pituitary adrenocorticotrophic hormone. (Abstr.), *Proc. Inst. Med. Chicago,* 18 (1950) 95-96.
83. D. J. Sandweiss, H. C. Salzstein, S. R. Scheinberg, and A. Parks, Hormon studies in peptic ulcer: pituitary adrenocorticotropic hormone (ACTH) and cortisone, *J. Am. Med. Assoc.,* 144 (1950) 1436-1442.
84. L. H. Sarett, A new method for the preparation of IT(a)-hydroxy-zo-ketopregnanes, *J. Am. Chem. Soc.,* 70 (1948) 1454-1458.
85. R. M. Shick, A. H. Baggenstoss, B. F. Fuller, and H. F. Polley, Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 492-494.
86. C. H. Slocumb: cited by P. S. Hench, in Ref. 39 *(m).*
87. L. J. Soffer, M. F. Levitt, and G. Baek, Use of cortisone and adrenocorticotropic

hormone in acute disseminated lupus erythematosus, *Arch. Internal Med.,* 86 (1950) 558-573.

88. I. F. Sommerville, G. F. Marrian, J. J. R. Duthie, and R. J. G. Sinclair, Abnormality in steroid metabolism associated with rheumatoid arthritis, *Lancet,* 1(1950) 116-117.
89. M. Sonenberg, A. S. Keston, and W. L. Money, Tracer studies with labelled preparations of anterior pituitary hormones: ACTH. *(Abstr.), J. Clin. Endocrinol.,* 10 (1950) 809.
90. D. M. Spain and N. Molomut, Effects of cortisone on the development of tuberculous lesions in guinea pigs and on their modification by streptomycin therapy, *Am. Rev. Tuberc. Pulmonary Diseases,* 62 (1950) 337-344.
91. T. D. Spies and R. E. Stone, Relief of the symptoms of acute gout and rheumatoid arthritis by means of pituitary adrenocorticotrophic hormone (ACTH), *Southern Med. J.,* 42 (1949) 720-722.
92. T. D. Spies and R. E. Stone, Pituitary adrenocorticotropic hormone (ACTH) as a tool of clinical and laboratory research, *Lancet,* 1 (1950) 11-14.
93. R. G. Sprague, M. H. Power, H. L. Mason, and H. E. Cluxton, Metabolic effects of synthetic compound E (17-hydroxy-II-dehydrocorticosterone) in two patients with Addison's disease and in one with coexisting Addison's disease and diabetes mellitus. (Abstr.), *J. Clin. Invest.,* 28 (1949) 812.
94. R. G. Sprague, M. H. Power, H. L. Mason, A. Albert, D. R. Mathieson, P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, Observations on the physiologic effects of cortisone and ACTH in man, *Arch. Internal Med.,* 85 (1950) 199-258.
95. E. Starling, Banquet address, Aug. 4, 1926, Congress of Physiology, Stockholm; cited by H. Theorell, in *Les Prix Nobel* en 1947, Stockholm, P. A. Norstedt & Söner, 1949, p. 40.
96. E. H. Steffensen, J. A. Olson, R. R. Margulis, R. W. Smith, and E. L. Whitney, The experimental use ofcortisone in inflammatory eye disease, *Am. J. Ophthalmol.,* 33 (1950) 1033-1040.
97. J. M. Stickney, F. J. Heck, and C. H. Watkins, Cortisone and ACTH in the management of leukemia and lymphoblastoma, *Proc. Staff Meetings Mayo Clinic,* 25 (1950) 488-489.
98. N. Svartz, The effect of ACTH on the agglutination with sensitized red sheep cells in rheumatoid arthritis, *Acta Med. Scand.,* Suppl. 246 (1950) 240-242.
99. Symposium on Urinary Corticosteroids, *Josiah Macy, Jr. Foundation Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Tenth Meeting,* New *York,* Josiah Macy, Jr. Foundation, 1945, pp. 125-220.
100. J. Tepperman, F. L. Engel, and C. N. H. Long, A review of adrenal cortical hypertrophy, *Endocrinology,* 32 (1943) 373-402.
101. G. W. Thorn, T. B. Bayles, B. F. Massel, P. H. Forsham, S. R. Hill, Jr., S. Smith III, and J. E. Warren, Studies on the relation of pituitary-adrenal function to rheumatic disease, New *Engl. J. Med.,* 241 (1949) 529-537.
102. G. W. Thorn, P. H. For&am, T. F. Frawley, S. R. Hill, Jr., M. Roche, D. Staehelin, and D. L. Wilson, The clinical usefulness of ACTH and cortisone, *New Engl. J. Med.,* 242 (1950) 783-793; 824-834; 865-872.

103. R. Tompsett, C. LeMaistre, C. Muschenheim, and W. McDermott, Effects of ACTH on tuberculosis in humans. (Abstr.), *J. Clin. Invest.,* 29 (1950) 849-850.
104. Upjohn-Penick, Expedition for botanical exploration: to Africa for cortisone precursors, *Scope*, 3 (1950) 4-9.
105. E. H. Venning; Adrenal function in pregnancy, *Endocrinology,* 39 (1946) 203-220.
106. E. H. Venning, M. M. Hoffman, and J. S. L. Browne, The extraction of cortin-like substances from human post-operative urine, *Endocrinology,* 35 (1944) 49-62.
107. L. E. Ward, C. H. Slocumb, H. F. Polley, E. W. Lowman, and P. S. Hench, Clinical effects of cortisone administered orally to patients with rheumatoid arthritis, *Proc. Staff Meetings Mayo Clinic,* 26 (1951) 361-370.
108. P. Weil and J. S. L. Browne, The excretion of cortin after surgical operation, *Science,* 90 (1939) 445-446.
109. N. L. Wendler, R. P. Graber, R. E. Jones, and M. Tishler, Synthesis of II-hydroxylated cortical steroids; 17(α)-hydroxycorticosterone, J. *Am. Chem. Soc.,* 72 (1950) 5793-5794.
110. M. J. Whitelaw, and T. W. Woodman, The treatment of severe burns with ACTH, *J. Clin. Endocrinol.,* 10 (1950) 1171.
111. W. Q. Wolfson, H. D. Hunt, C. Cohn, W. D. Robinson, and I. F. Duff, ACTH and colchicine in the clinical treatment of acute gouty arthritis. Physiological considerations and review of therapeutic results in fifty-one attacks, *J. Michigan Med. Soc.,* 49 (1950) 1058-1064; 1083.
112. W. Q. Wolfson, R. E. Thompson, W. D. Robinson, H. D. Hunt, C. Cohn, E. E. Hayes, R. C. Levy, S. L. Pearlman, B. B. Rubenstein, W. Wise, and I. Zitman. Physiologic and clinical studies with long-acting preparations ofpituitary adrenocorticotrophic hormone, *Univ. Michigan Med. Bull.,* 16 (1950) 152-163.
113. A. Zaffroni, R. B. Burton, and E. H. Keutmann, Adrenal cortical hormones : analysis by paper partition chromatography and occurrence in the urine of normal persons, *Science,* III (1950) 6-8.