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The development of cortisone as a therapeutic agent

Nobel Lecture, December 11, 1950

The first investigations which contributed to the development of cortisone came in 1929 from physiologists. Two groups of workers, Hartman and his associates[1] at the University of Buffalo, and Swingle and Pfiffner[2] at Princeton University, were the first to prepare extracts from the adrenal cortex which successfully controlled the symptoms of adrenal insufficiency both in adrenalectomized animals and in patients who had Addison's disease.

Cortisone was first separated as a new compound in 1935[3]. Investigations concerned with the isolation and determination of the chemical structure of cortisone were carried out simultaneously and independently by Winter-Steiner and Pfiffner[4] at Columbia University, by Reichstein and his associates[5] at Zurich, Switzerland, and by my associates and myself at the Mayo Clinic[6].

From the beginning of the investigation at the Mayo Clinic the work has been carried out by an able group of associates. At this time it is a pleasure to recognize the contributions made to both the theoretical and technical aspects of the many problems by my colleagues, among whom are Lewis L. Engel, Gerard A. Fleisher, Warren F. McGuckin, Bernard F. McKenzie, Harold L. Mason, Vernon R. Mattox and Richard B. Turner.*

The number of different compounds eventually separated from the adrenal cortex[7] was 28. All these compounds belong to the family of steroids and all are closely related one to the other. For the detailed investigation of this large group of compounds, science is indebted to the very significant contributions which have come from the laboratory of Professor Tadeus Reich-

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* Essential contributions to our knowledge of the physiological significance of the adrenal cortex came from the work of Dr. Frank C. Mann who performed the operations for adrenalectomy. Drs. Benjamin B. Wells and Roger M. Reinecke demonstrated the influence of the adrenal cortex on the metabolism of protein and carbohydrates. Dr. Dwight J. Ingle carried out the important work on the relation between the adrenal cortex and activity of the muscle. Drs. William D. Allers, Hugo Nilson, and Joseph Svirbely studied the metabolism of electrolytes in adrenalectomized animals and Donald Krockow was responsible for care of adrenalectomized animals. Drs. Willard M. Hoehn, Charles S. Myers, Harold R. Nate, Frank Stodola, and Eugene L. Woroch have contributed to chemical phases of the investigation.

stein. Some of these compounds contained two, some three, some four, and a few contained five atoms of oxygen in the molecule. In certain of these steroids there was a double bond adjacent to a ketone, and this small group of compounds soon acquired special interest because they were the only ones which possessed physiologic activity. If the double bond was removed, the physiologic activity was abolished[8]. This fact focused attention on four compounds which were designated in my laboratory as A, B, E, and F. Because of the limited supply, it was decided that all of the material separated from the gland should be used on small animals and that none should be employed for investigations in clinical medicine.

Work on the adrenal cortex at first was confined to a few physiologists, and several years were required to accumulate evidence concerning the physiologic activity of these compounds. Eventually, it was shown that compounds A, B, E, and F had little effect on the metabolism of electrolytes but that they had marked influence on the metabolism of carbohydrates and protein[9]. In addition, it was found that the muscles in adrenalectomized animals soon lost the power to contract when they were stimulated, but that these compounds would restore the ability of the muscle to respond[10]. Finally, it became evident that the adrenalectomized animal could not resist in the normal manner toxic substances such as typhoid vaccine. Compounds A, B, E, and F restored the resistance of the animals to these toxic substances[11] (Fig. 1).

On the basis of these experiments on animals the hope was raised that these compounds from the adrenal cortex might be of help to patients who had suffered trauma including burns or who had certain types of infection. But when this hypothesis was tested with extracts of the adrenal cortex encouraging results were not obtained. Today some of these failures can be explained, but at the time they were accepted at face-value. For many years there were few who believed that any product of the adrenal cortex would find a place in clinical medicine other than in the treatment of the relatively few patients who had Addison's disease. Under these conditions, it is not surprising that pharmaceutical manufacturers were not interested in the commercial aspects of the adrenal cortex.

In October, 1941, this situation changed suddenly and completely. The shadow of war was advancing and the medical departments of the army and navy approached the National Research Council of the United States with the request that the hormones of the adrenal cortex be made available. The National Research Council called a conference of those interested in the field,

and a serious attempt was made to prepare the hormones of the adrenal cortex by partial synthesis from some material which could be obtained on a large scale. At the first conference in October, 1941, the agenda called for a discussion of the best way to proceed. Which of the four compounds A, B, E, and F should be the objective? There was a consensus that the objective should be compound A. The reason for this was that of the four substances, compound A possessed the simplest chemical structure.

The least complicated member of the pregnane series, desoxycorticosterone, had been made in 1937 by Steiger and Reichstein[12] and was found to
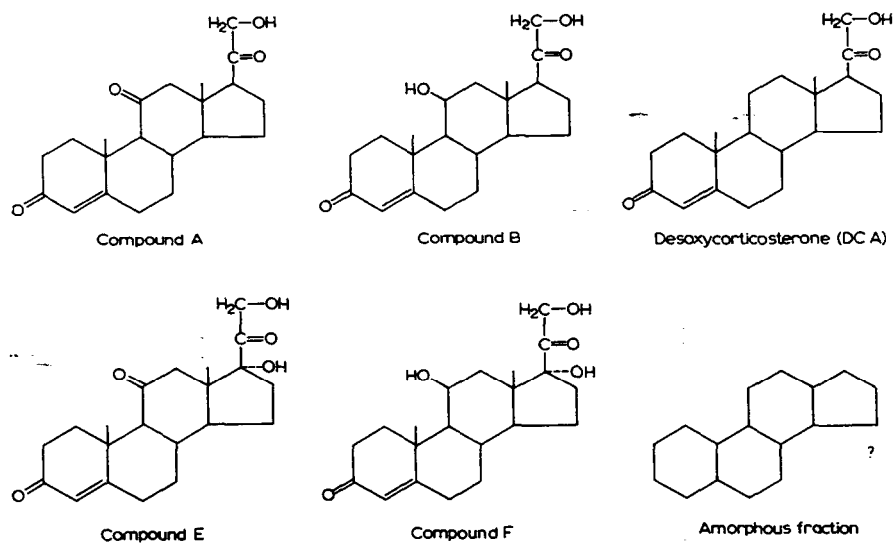

Fig. 1. Structural formulas of compounds A, B, E, F and desoxycorticosterone. Compounds E and F are identical with A and B respectively, except for the presence of an additional hydroxyl group at position 17. Desoxycorticosterone-does not possess a substituent either at 11 or 17.

influence the metabolism of sodium, potassium, chloride, and water; but it also had been shown that desoxycorticosterone did not appreciably affect the activity of muscle or the metabolism of carbohydrate and protein[13-16].

There are three atoms of oxygen in desoxycorticosterone. The next more complicated chemical structure is that of compound A which is identical with desoxycorticosterone except that it has an atom of oxygen at position 11. Compound E is still more complicated. This hormone is identical with compound A except for the presence of a fifth atom of oxygen[7] at position 17.

Under these circumstances the most practical procedure was first to make compound A, for unless this was accomplished there was but little hope that compound E could be made in satisfactory yield.

I shall not describe the strenuous efforts expended in many laboratories to make compound A. Different avenues of approach were tried, starting materials obtained from yeast, plants, and bile were used, information was exchanged at a series of conferences, but for three years all attempts in the United States to make compound A failed.

In Switzerland, Lardon and Reichstein[17] prepared the first sample of compound A from desoxycholic acid but the method which they used could not be employed on a large scale. Someone has said that of all the projects sponsored by the National Research Council, the work on the hormones of the adrenal cortex was the least productive. This, however, is not true. The investigations carried out furnished experience and contributed essential information which subsequently made possible the manufacture of compound E on a factory scale.

Compound A was produced by a practical method devised in my laboratory[18] in 1944. Merck and Co., Inc., using the same method, prepared a large sample of this compound in 1945. It was tested on adrenalectomized laboratory animals and was found to have physiologic activity identical with compound A which had been isolated from the adrenal glands of beef [19-22].

Now, for the first time, it was possible to test this compound on a satisfactory scale in clinical medicine. The condition in which it should be of most value was Addison's disease. Considerable interest surrounded this first utilization of one of the compounds of the adrenal cortex which had been prepared from starting material other than adrenal glands.

The patient was closely observed by Dr. Randall G. Sprague and his associates and the results were clear. Compound A had but little influence either subjectively or objectively on the symptoms of Addison's disease[23]. After all the work that had been expended, this result came as a surprise and was a great disappointment.

In 1946 it was generally believed that the four compounds, A, B, E, and F, closely resembled each other in physiologic activity. It was believed also that larger doses of A and B were required than of compounds E and F to produce the same effect. At that time it could not be anticipated that within two years convincing evidence would be obtained which would show that compounds E and F possessed activity not shared with compounds A and B. Neither could it be foreseen that this essential information would come not

from experiments on animals but from work with patients. Yet before this information could be obtained it was necessary for the chemist to make compound E in suitable amounts.

In spite of the disappointing results that had been obtained with compound A, attempts to convert a compound closely related to compound A into compound E were carried out both in the laboratories of the Mayo Foundation and in those of Merck and Co., Inc. Dr. Lewis H. Sarett, in the research laboratory of Merck and Co., Inc., first accomplished this conversion, and in the summer of 1947 it became evident that a practical method to make compound E soon would be available[24]. From that time onward the work progressed smoothly. The first few grams of compound E made their appearance in May, 1948, and more was produced during the summer.

Merck and Co., Inc. was faced with the problem: To whom should this material be given and how should these first few grams be used? For many months no satisfactory answer was found and this fact now furnishes a clear demonstration of how little was known in 1948 about the function of the adrenal cortex.

Although little was known, there was much speculation, and among those who speculated were Dr. Philip S. Hench and myself.

In 1929 Dr. Hench had observed that the painful symptoms of rheumatoid arthritis were relieved in a patient who developed jaundice, and in 1931 he was equally impressed when another patient was also relieved after she became pregnant. Throughout the following years these clinical observations were augmented and provided evidence that rheumatoid arthritis was not always a relentless, progressive disease.

Dr. Hench believed that rheumatoid arthritis is a reversible condition. He suggested that some agent which he designated substance X was present during jaundice and in pregnancy, and that through the influence of substance X the symptoms of rheumatoid arthritis were relieved. Dr. Hench sought the help of others in an attempt to identify substance X, and during the past 12 years we have had many conferences. After one of these conferences in January, 1941, when a decision was reached to employ compound E in rheumatoid arthritis, Dr. Hench made an entry to this effect in a notebook. We did not realize that seven years would pass before compound E would become available in amount sufficient to permit its use in clinical medicine but neither of us forgot the decision made in 1941.

I have described the result of administration of compound A to a patient who had Addison's disease as a great disappointment. However, this ex-

perience with compound A made it possible to use compound E successfully. Three things became evident: (1) Because of the insolubility of compound E acetate* it was desirable to use the hormone in its free form, not as the acetate. (2) The material should be injected as an aqueous suspension which would be absorbed over a long interval and thus furnish a continuous supply of the hormone. (3) The crystals should be ground to a fine powder to insure absorption at a satisfactory rate. Large crystals would resist absorption for several days.

During the summer of 1948, compound E was administered in this manner by Dr. Sprague of the Mayo Clinic to a patient who had Addison's disease, and the result was encouraging. There was a notable improvement in the condition of the patient.

A short time after this, Dr. Hench once more asked the question, "When will compound E be available", and I replied that at last it soon would be ready for his use. On September 21, Dr. Charles H. Slocumb, Dr. Hench's associate, administered the first injection of this hormone to a patient who had rheumatoid arthritis. During the following seven months compound E was given by Dr. Howard F. Polley, another associate of Dr. Hench, to many more patients who had rheumatoid arthritis and rheumatic fever and the adrenocorticotropic hormone of the anterior portion of the pituitary body also was shown to produce similar result[25].

I shall not describe in detail the wide expansion of the use of compound E. One immediate result was to produce confusion in the minds of some, concerning the relation between vitamin E and compound E of the adrenal cortex. It seemed desirable to give compound E a distinctive name and the word cortisone was chosen.

To tell the full story of the development of cortisone as a therapeutic agent it will be nececessary to go back to the last months of 1944. At that time the first few milligrams of cortisone acetate were made by Dr. Sarett[26] in the research laboratory of Merck and Co., Inc. Although the method which he used could not be employed for large-scale production because of the very low yield, nevertheless it was taken as a basis for calculating the amount of starting material which would be required to make just 5 g of cortisone. This was most fortunate because it ensured the use of a large amount of starting material. It was also most fortunate that during 1947 and 1948 several important improvements of some of the steps in the preparation of com-

* Later it was found that finely ground compound-E acetate (particle size 5-10 microns) was absorbed at a satisfactory rate.

pound A were made in my laboratory[19,27]. Moreover Dr. Sarett made an essential contribution for the conversion into cortisone of a compound closely related to compound A - a new method[24] of introducing the hydroxyl group at C(17).

The result was that instead of the calculated 5 grams of cortisone, a total of 400 grams became available, and when requests for cortisone continued to come from the Mayo Clinic, Merck and Co., Inc. could continue to supply the hormone, although at a limited rate. In so far as the clinical results are concerned this is the most important single fact which stands out in retrospect. With the amount of cortisone made available it was possible within a few months to obtain convincing evidence. With less material this would have been impossible.

All the cortisone which had been prepared by Merck and Co., Inc. had been made on the laboratory or small pilot plant scale. The question then arose as to whether the company now should enlarge the facilities to large pilot plant and factory scale. There was one good reason why they should expand the manufacture of cortisone. There were five good reasons why they should not. The one good reason was the demand for cortisone. Opposed to this were: (1) The uncertainty of the future: how great would be thedemand and how long would it continue? (2) No compound as complex as cortisone had ever been made on a factory scale. The venture would be without precedent. (3) For a long time the cost of manufacture would be high and the volume of sales would be small because of the price. A large amount of money would have to be invested. (4) The patent situation which eventually would control the manufacture of cortisone by Merck and Co., Inc. and three other companies was complicated, confused and to many it seemed hopeless. (5) Why not find something else as a substitute for cortisone, something just as good?

You now know that Merck and Co., Inc. accepted the challenge, devised apparatus with which cortisone could be made on a large scale, and above all demonstrated that sound scientific endeavor and fortitude can find answers to the most complicated and discouraging problems.

To chemists, physiologists, and clinicians the results have brought assurance and stimulation. For many patients hope has displaced despair. Progress in the manufacture of cortisone can be illustrated by its price. In July, 1949 the price per gram was $200.00 and this continued until after January, 1950. Since that time the price has been reduced five times: to $150.00, $135.00, $95.00, $50.00, and on November 1, 1950, to $35.00. Furthermore, in

1949 the supply of cortisone was allocated by a committee appointed by the National Academy of Sciences, but today it is available to every physician in the United States.

The five questions which were cited as reasons why the large-scale manufacture of cortisone should not be undertaken in 1949 have all been answered. The answers to the first three are obvious. The patent problem, number (4), has been solved by the Research Corporation of New York through an agreement among four large manufacturing companies and the Research Corporation. This agreement allows the mutual use of all patents.

The answer to question (5) will require brief discussion. It has been mentioned that in 1948 it was expected that cortisone would be employed for the treatment of Addison's disease and that it might be useful in trauma including burns and in some types of infection, but the demonstration that cortisone would have wide application in rheumatoid arthritis, rheumatic fever, and in the collagen diseases came as a surprise to many of those interested. This demonstration produced a situation which was quite different from the sequence of events associated with the isolation and use of the hormones from other glands of internal secretion.

For example: An extract of the adrenal medulla was known to increase blood pressure and no one was surprised when crystalline epinephrine was shown to do the same thing. Desiccated thyroid substance increased the basal metabolic rate, and crystalline thyroxine possessed this same activity. An extract of the pancreas lowered the concentration of blood sugar, and crystalline insulin is standardized by determination of its effect on blood sugar. But no one had shown that an extract of the adrenal cortex could influence the symptoms of rheumatoid arthritis, rheumatic fever and asthma, and when it was announced that cortisone possessed unusual physiologic activity which was not associated with any known function of the adrenal cortex, there was a tendency to regard cortisone not as a hormone of the adrenal cortex but rather as a pharmacologic agent which was a member of a large and well-known group of compounds - the steroids.

This viewpoint, taken together with the element of surprise, immediately led many investigators to believe that other surprises were just around the corner and that many other compounds would be found which were as good as or better than cortisone. This trend was unfortunate for it tended to remove cortisone from its rightful place among those few agents which are recognized as hormones. Epinephrine, thyroxine, insulin, and parathyroid hormone are physiologically active compounds which Nature has developed

and used during past ages; something just as good has not been found to replace any one of them. It is highly improbable that any product ever will be found which can be used in place of cortisone and the closely related compound F. At any rate, no substitute is known today, and all of the most promising compounds have been tested[28](Figs. 2, 3, 4, and 5).

Cortisone now is being produced at a rate of many kilograms a month by Merck and Co., Inc. To the present all of it has been prepared from the bile of beef and sheep. There is a limit, however, to the amount of bile that can be collected, so that other more abundant starting material must be found. The next most likely source for starting materials are compounds found in plants, and some of those grown in Mexico may be used in the near future.

The most satisfactory method for the production of cortisone would be by total synthesis from simple organic compounds, but to build up cortisone from such material is a major problem in organic chemistry, and it will require patient and persistent labor for several years. I am confident, however, that it will be accomplished.

Improvements in the process for the preparation of cortisone from bile may be expected. I have already mentioned that in 1947 Dr. Sarett discovered a practical procedure for the introduction of a hydroxyl group at position 17 (Fig. 6). My associates, Drs. Colton, Nes, Van Dorp, Mason, and I now have found another series of reactions by which this step can be accomplished [29], and I refer to it now because it illustrates in a striking manner the interplay of forces which influence the reactivity of various parts of the steroid nucleus.

When pregnanolone with the ketone group at $C_{(20)}$ is brominated the first substitution with bromine is at $C_{(17)}$. But if the same compound with an additional ketone group at $C_{(11)}$, an atom of bromine at $C_{(12)}$ and an acetate group at $C_{(21)}$ is brominated, the first atom of bromine enters at $C_{(21)}$. The second atom of bromine apparently substitutes the atom of hydrogen at $C_{(17)}$ but the presence of the substituents at 11, 12, and 21 activates this atom of bromine to such an extent that dehydrobromination and formation of a double bond Δ^{16} occurs spontaneously. This in turn increases the reactivity of $C_{(15)}$, and bromine is substituted for hydrogen at this position. The product is a 12,15,21-tribromo compound which is highly reactive and furnishes a short and convenient method for introduction of the hydroxyl group at $C_{(17)}$ without the use of osmium tetroxide (Figs.7, 8, 9).

Desoxycorticosterone acetate

Pregnenolone

21-Acetoxy-pregnenolone

Cortisone acetate

Reichstein's "S"

Pregnentriolone

Fig. 2.

17-Hydroxyprogesterone

21-Desoxy E

Compound A
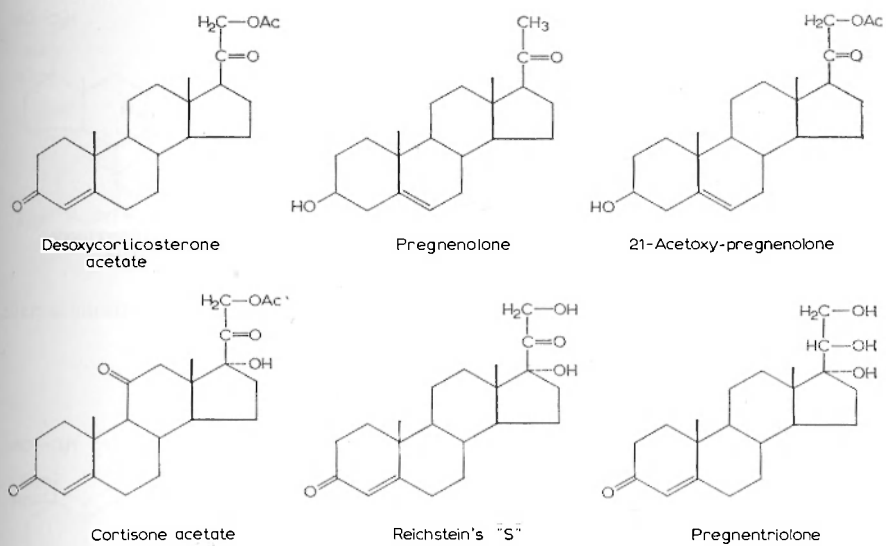
Compound E

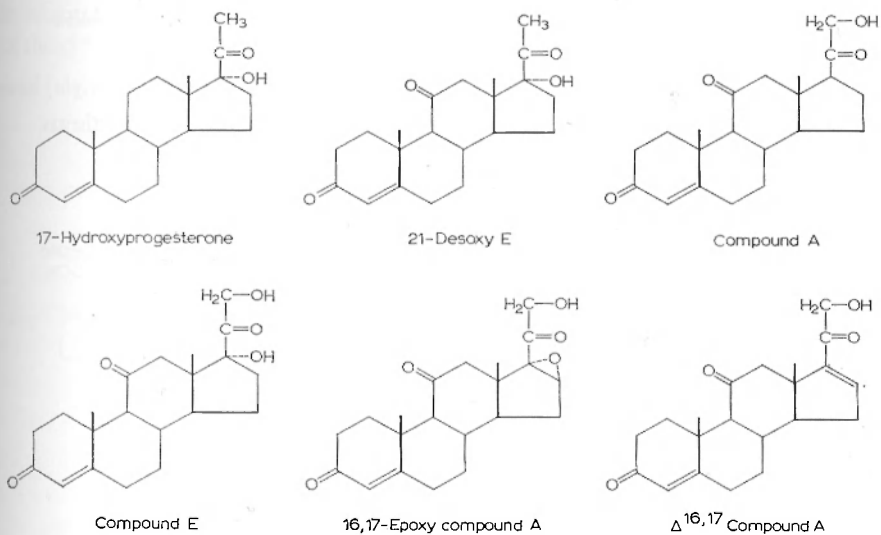16,17-Epoxy compound A

$\Delta^{16,17}$ Compound A

Fig. 3.

Figs. 2 and 3. Structural formulas of ten compounds closely related to compound E which have been shown not to affect symptoms of rheumatoid arthritis. The formulas for compound E and its acetate (cortisone acetate) are included for purposes of comparison.
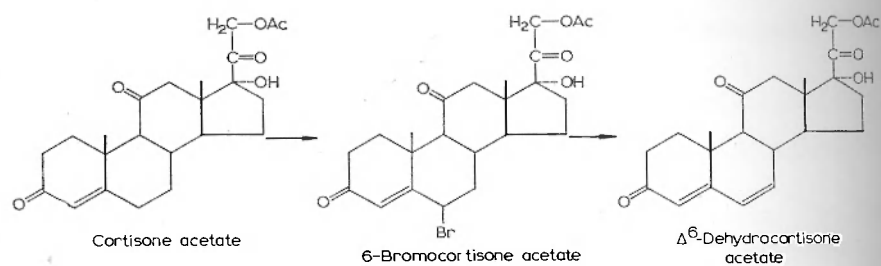
Fig. 4. Preparation of Δ^6-dehydrocortisone acetate through 6-bromocortisone acetate.
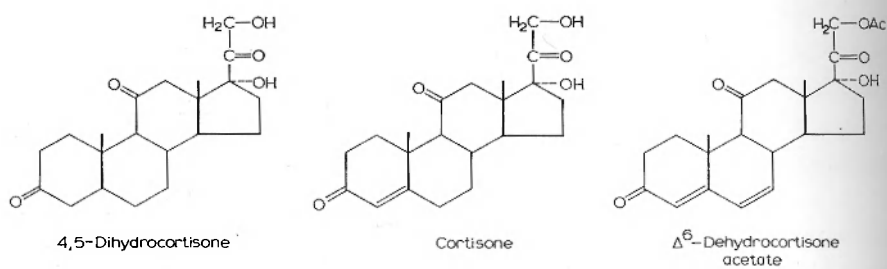

Fig. 5. Neither 4,5-dihydrocortisone (*left*) nor Δ^6-dehydrocortisone acetate (*right*) have physiologic activity when tested on patients who have rheumatoid arthritis.
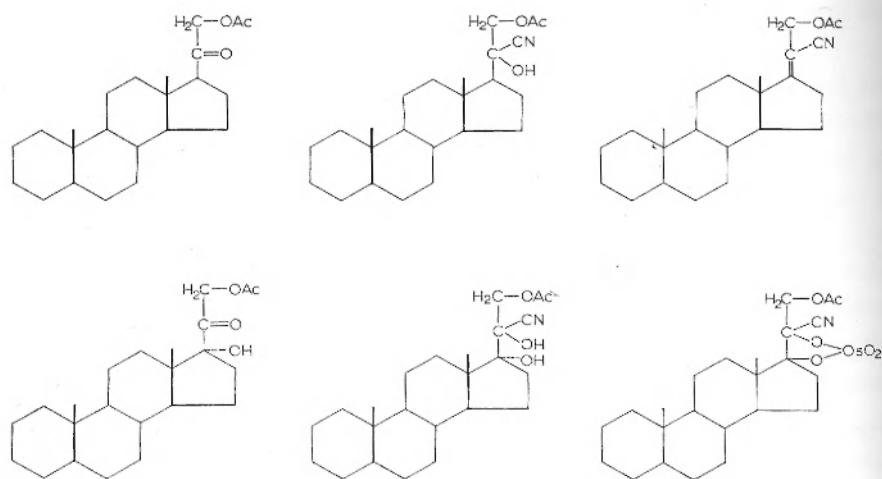

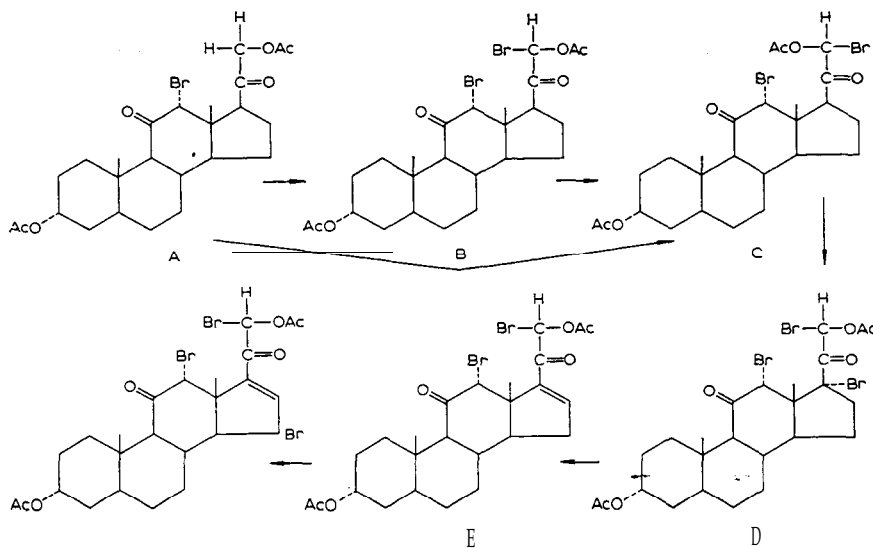Fig. 6. Sequence of steps used by Sarett to introduce a hydroxyl group at $C_{(17)}$.

Fig. 7. Bromination of 3α,21-diacetoxy-11,20-diketo-12α-bromopregnane in anhydrous acetic acid with hydrogen bromide as catalyst affords two diastereoisomeric compounds B and C with bromine at positions 12 and 21. Further bromination results in substitution presumably at 17 (Formula D), and dehydrobromination with formation of the Δ^{16} double bond (Formula E). Position 15 is then readily substituted to give the 12α,15,21-tribromo compound (Formula I).
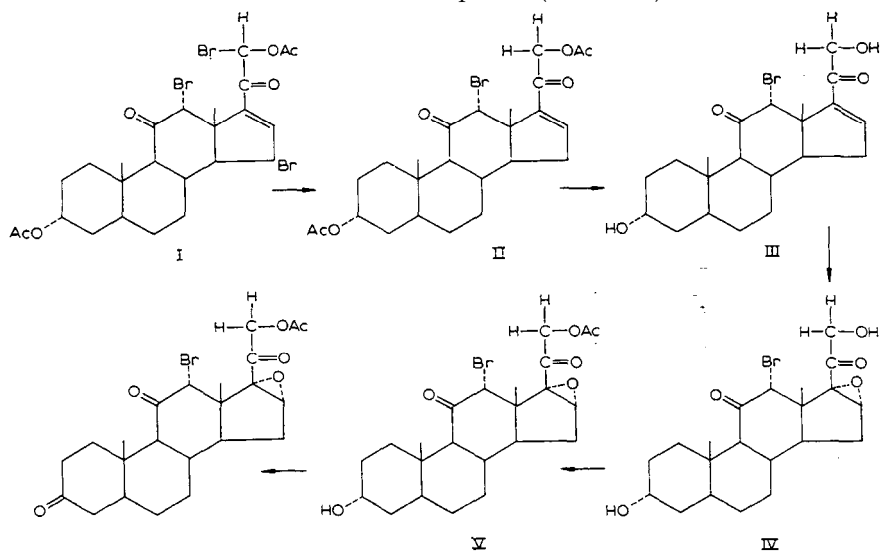

Fig. 8. The tribromo derivative (I) is reduced with hydriodic acid with loss of two atoms of bromine (II). Deacetylation in boiling dilute aqueous methanolic hydrochloric acid affords the 3α,21-dihydroxy compound (III) which is epoxidized (IV), acetylated at C(21) and oxidized at position 3.
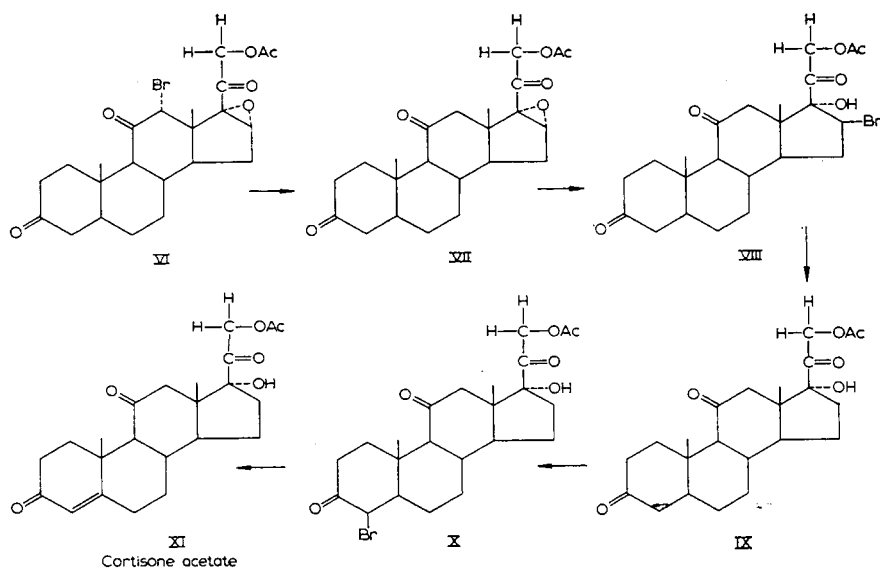
Fig. 9. Reductive removal of the bromine at $C_{(12)}$ is necessary to permit cleavage of the 16,17-epoxide with hydrogen bromide to give VIII. Similar removal of the bromine at $C_{(16)}$ affords 4,5-dihydrocortisone which is readily converted into cortisone by bromination at $C_{(4)}$ and dehydrobromination through formation of a hydrazone at $C_{(3)}$.

The other four alterations by which desoxycholic acid is converted into cortisone are shown in Figs. 10, 11, 12, 13, and 14. Crystalline cortisone is shown in Fig. 15.

I shall venture a word about the future place of cortisone in clinical medicine. There is no doubt that the use of this hormone of the adrenal cortex will continue to increase. Its effect is unique in rheumatoid arthritis, rheumatic fever, asthma and hay fever, and other allergic conditions You also are familiar with the use of cortisone in periarteritis nodosa, lupus-erythematosus, pemphigus, psoriasis, and other intractable skin diseases, iritis and other diseases of the eye[30]. I shall not discuss the clinical phases of cortisone in detail but I should like to report on a recent important advance in the method of administration of this compound, namely by mouth.

Many years ago the observation was made in my laboratory that an extract of the adrenal cortex added to the drinking water of adrenalectomized rats was more effective than the same amount of extract given by injection. It has now been shown, at the Mayo Clinic and elsewhere, that 100 mg of cortisone given by mouth in four tablets of 25 mg each throughout the day
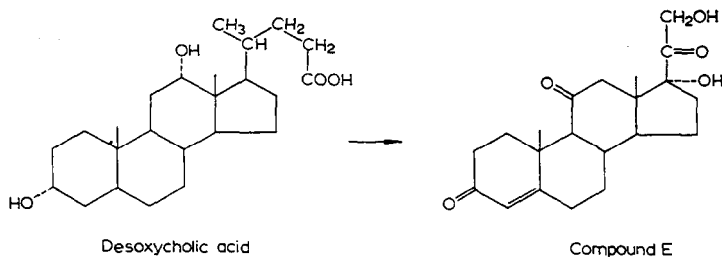
Fig. 10. The conversion of desoxycholic acid involves five alterations. These are indicated in Figs. 11, 12,13, and 14.
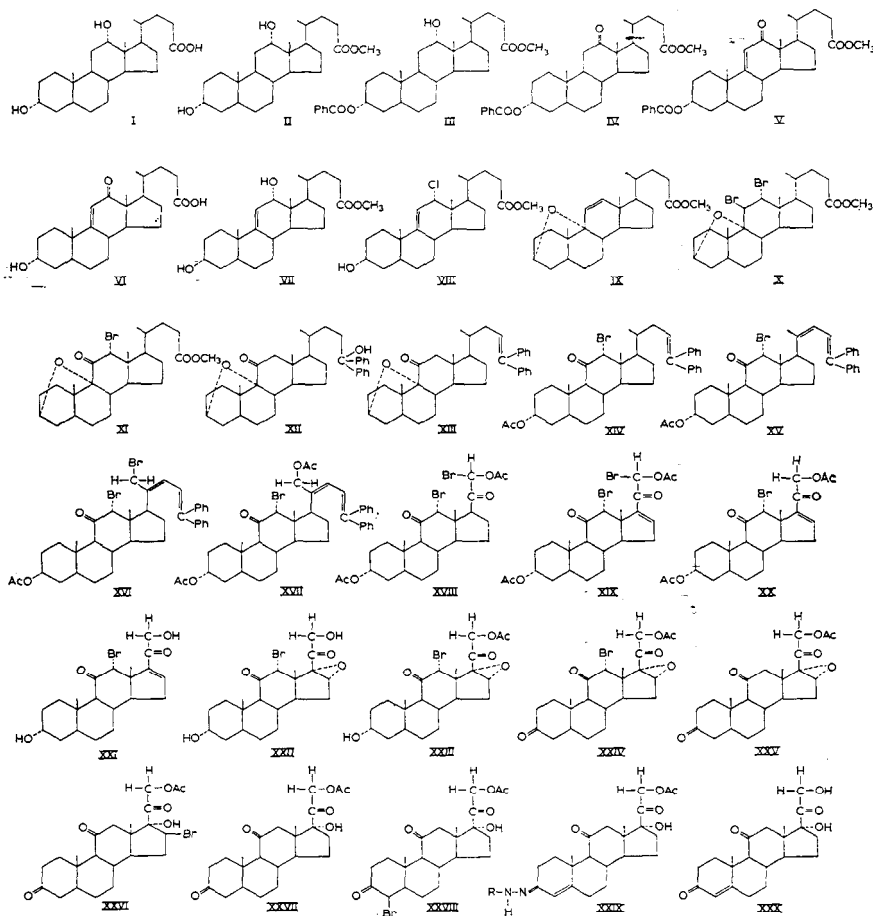

Fig. II. The preparation of cortisone from desoxycholic acid requires thirty steps.
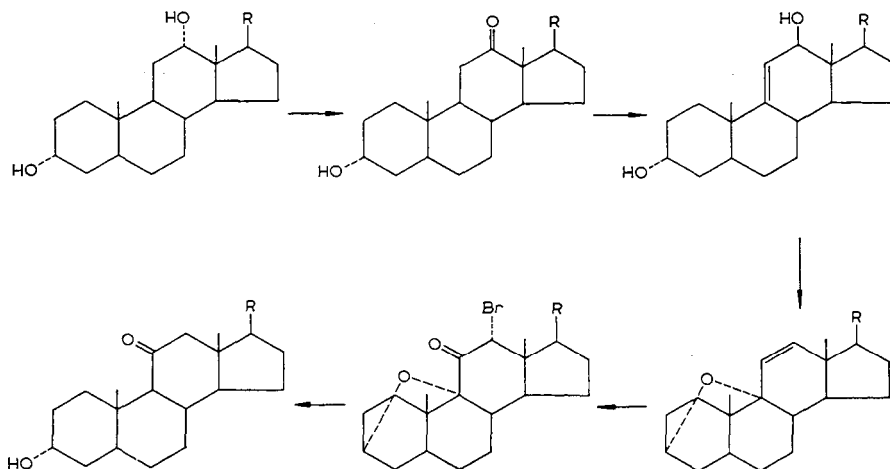
Fig. 12. *Alteration 1.* Removal of oxygen from C(12) and introduction of oxygen at C(11). The hydroxyl group at C(3) of methyl desoxycholate is benzoylated, the hydroxyl group at C(12) is converted to a ketone and the $\Delta^{9,11}$ double bond is formed with selenium dioxide. After hydrolysis in dilute warm alkali the **3α-hydroxy-12-keto-$\Delta^{9,11}$-cholenic** acid is separated and esterified with methanol. Reduction of the C(12) ketone to the hydroxyl group and treatment in a cold two-phase system of chloroform and concentrated hydrochloric acid replaces the C(12) hydroxyl group with chlorine. Dehydrochlorination in the same solvent with aqueous sodium bicarbonate forms the 3,9-epoxide with Δ^{11} double bond. Bromination affords a dibromo derivative in which the atom of bromine at C(11) is almost quantitatively replaced by the ketone group and the bromine at C(12) is not affected. After removal of the bromine at C(12) either with zinc or by the Grignard reagent during formation of 24,24-diphenyl-das-cholene, the 3,9-epoxide is opened with hydrogen bromide at 0°. The product is methyl **3α-**hydroxy-II-keto-12a-bromocholanate　　or　　3a-hydroxy-II-keto-12a-bromo-24,24-di-**phenyl-Δ^{23}-cholene.**

is just as effective as 100 mg of cortisone given in one dose in the muscle[32]. This observation is difficult to explain unless a large part of the injected material is absorbed rapidly and excreted rapidly. Absorption from the alimentary tract may be less efficient but nevertheless the distribution and utilization of cortisone in the body may be more uniform and continuous when it is given by the enteral route. It is intended to investigate the factors involved, but whatever the final explanation, oral administration of cortisone will be welcomed by both patient and physician.

There is another important aspect relating to the method of administration which should be mentioned. I refer to so-called side reactions. It is to be expected that large amounts of cortisone injected daily are more likely to pro-
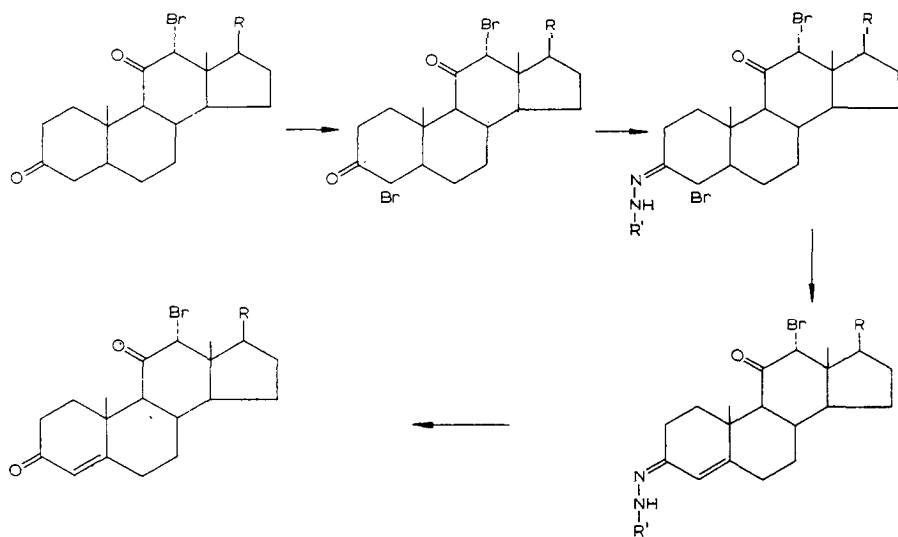
Fig. 13. *Alterations 2 and 3.* Removal of side chain and formation of 20,21-ketol acetate. The 24,24-diphenyl-12α-bromO-Aza-cholene is brominated at $C_{(22)}$ and dehydrobrominated to form the diene structure in the side chain. The presence of the diene increases the reactivity of $C_{(21)}$ which is readily brominated with bromosuccinimide. The $C_{(21)}$ bromo compound is converted to the 21-acetate and ozonation affords **3α,21-diacetoxy-11,20-diketo-12a-bromopregnane**. The formation of the diene and oxidative removal of the side chain[31] is the only step not devised in the laboratory of the Mayo Foundation.

duce the signs and symptoms of overdosage than are minimal effective doses administered more frequently. It has been observed that when cortisone has been given orally in tablets of 25 mg each, the significant signs of overdosage may not appear even after prolonged administration.

On November 1, 1950, cortisone was made available to physicians of the United States through drug supply houses. It then assumed its place as a therapeutic agent among the many other new drugs which recently have been developed. But cortisone will be unique, for it is new only in the sense that it has been made available. From the time, ages ago, when cortisone was first made in the adrenal cortex it has continued to serve as a powerful agent in health and disease. Today the chemical structure of cortisone is known in every detail but one more chapter remains to be written. What physiologic processes are modified by cortisone and how this influence is exerted are matters still locked within this hormone of the adrenal cortex. Said Shakespeare's soothsayer, "In Nature's infinite book of secrecy a little I can read."

Fig. 14. *Alteration 4.* Formation of a Δ^4 double bond. Bromination at $C_{(4)}$ and dehydrobromination through the activating influence of the 2,4-dinitrophenylhydrazone at $C_{(3)}$ followed by restoration of the ketone group with pyruvic acid affords cortisone.
    Alteration 5. Introduction of a hydroxyl group at $C_{(17)}$ is described (Figs. 7,8,9).

Fig. 15. Crystals of cortisone.

1. F. A. Hartman and K. A. Brownell, The hormone of the adrenal cortex, *Science,* 72 (1930) 76.

2. W. W. Swingle and J. J. Pfiffner, The revival of comatose adrenalectomized cats with an extract of the suprarenal cortex, *Science,* 72 (1930) 75-76.

3. H. L. Mason, C. S. Myers, and E. C. Kendall, The chemistry of crystalline substances isolated from the suprarenal gland, *J. Biol. Chem.,* 114 (1936) 613-631.

4. O. Wintersteiner and J. J. Pfiffner, Chemical studies on the adrenal cortex. III. Isolation of two new physiologically inactive compounds, *J. Biol. Chem.,* 116 (1936) 291-305.

5. T. Reichstein, Über Bestandteile der Nebennieren-Rinde. VI. Trennungsmethoden sowie Isolierung der Substanzen Fa, H und J, *Helv.Chim. Acta,* 19 (1936) 1107-1126.

6. 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) 459-474.

7. T. Reichstein and C. W. Shoppee, The hormones of the adrenal cortex. In R. S. Harris and K. V. Thimann, *Vitamins and Hormones,* Academic Press, New York. 1943, vol. I, PP. 345-413.

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