1950

Experimental therapy of rheumatoid arthritis with cortisone (Compound E)

Vernon Hayes Cutshall
University of Nebraska Medical Center

EXPERIMENTAL THERAPY OF RHEUMATOID ARTHRITIS WITH CORTISONE (COMPOUND E)

Vernon H. Cutshall

Senior Thesis

Presented to the College of Medicine

University of Nebraska

Omaha, 1950

EXPERIMENTAL THERAPY OF RHEUMATOID ARTHRITIS WITH CORTISONE (COMPOUND E)

For generations the human race has suffered mildly to intensely the effects of the disease known as rheumatoid arthritis, and for just as long nearly every imaginable type of therapy has been tried in an effort to relieve the distressing symptoms of patients so suffering, most of which, to no avail or to give just mild transient relief. Perhaps the main reason no specific therapy has been found satisfactory, is because the basic etiology is disputed, doubtful, or even unknown. Thus because of the great resistance of this disease to treatment a rejuvenation took place in the medical profession regarding rheumatoid arthritis when cortisone (compound E) was found to give prompt relief of symptoms and signs of this disease. Further interest was created due to the fact that light has now been thrown on the etiology of this disorder and of other diseases, heretofore, whose causes have remained unknown for the greater part. While all therapy with compound E, up to date, has been experimental in a short time such therapy will probably be placed on a practical basis.

ANTECEDENT WORK

The suspicion that a hormonal-biochemical inbalance might be the cause of rheumatoid arthritis has become more persistent in recent years. Seyle [21], in his "adaptation

syndrome" hypothesis, lends support of its being an endocrine dysfunction. Experiments have been undertaken in support of this theory, which explains certain chronic diseases on the basis that they are perverted and abnormal adaptations to unfavorable environmental circumstances mediated through the endocrine system. Only a few facts regarding the physiology have been established due to limitation of supply of this substance. Compound E was used in experimentation with rats and it was noted in rats subjected to adrenalectomy, muscle activity increased demonstrably and physiologic resistance to stress, cold, and certain toxic substances also was increased. [11,15] In young rats (male and female) given compound E, suppression of growth was immediate and pronounced.[24] Administration of the substance to normal rats produced a transient hyperglycemia and glycosuria, and when given to partially depancreatized rats, there was an intensification of the diabetic state.[10,12]

The occurrence of rheumatoid arthritis has been noted frequently in various endocrinopathies [2] (diabetes insipidis, acromegaly, myxedema, eunuchoidism, dwarfism, adiposogenital dystrophy, menopause) reported in the literature. The coincidence between arthritis and endocrinopathy seems to be more frequent than would be anticipated if the two disorders were unrelated. Pregnancy and jaundice, it has been observed in a number of cases, very

often cause a marked remission of rheumatoid arthritis. Hench has made an intensive study of effects of pregnancy and jaundice and their relationship to rheumatoid arthritis.[8] In 1938 he made observations on thirty-four pregnancies of twenty patients with this disease. Thirty of these pregnancies produced marked or complete remission of the arthritis. In one hundred and fifty rheumatoid patients, results of pregnancy in its effect on rheumatoid arthritis was later studied by Hench, Slocumb, and Polley.[8] They noted that the disease rarely began during the course of pregnancy and if so, it was for a brief period only. Also, rheumatic patients relieved once by pregnancy were almost always relieved of their rheumatic symptoms by subsequent intra-uterine pergnancies. Even in the women who habitually miscarried at the second or third month of gestation, marked or complete relief of articular symptoms was obtained about one month prior to the miscarriages. This relief usually began about the fourth to sixth week of pregnancy and lasted until one to seven weeks post-partum in nearly all cases. In these cases pain subsided almost completely; tenderness disappeared notably or completely, articular swelling was greatly reduced and muscle stiffness disappeared or markedly decreased.

Another accidental remission of rheumatoid arthritis was observed by Hench in patients with jaundice. Since 1929 he has seen the two conditions in thirty patients,

twenty-five of whom experienced marked or complete temporary remission of the arthritis irrespective of the concentrations of bilirubin in serum.[8] Holbrook[9] collected from the literature and from questionnaires sent to various rheumatologists a total of eighty-four cases of rheumatoid arthritis in which jaundice supervened. Sixty-four per cent of these patients showed marked remission. Hemolytic jaundice appears to be ineffective but in the direct reaction types of jaundice in which there had been enough liver damage to give a notable bilirubinemia, there were numerous instances of remissions of the arthritis. These remissions lasted from one month to two years whereas the effective jaundice lasted an average of eight weeks.

Because of the potential reversibility of rheumatoid arthritis as noted above, a revision has to be considered in the diagnosis, prognosis, and treatment of the disease. Any theory on the etiology of rheumatoid arthritis has to take into consideration the ameliorative influence of jaundice and pregnancy; therefore it seems likely that there is a biochemical disturbance of still unknown type which is accidentally and transiently corrected by some biological-hormonal change common to a number of apparently unrelated events, most notable of which are jaundice and pregnancy.

Therapeutic procedures have been based on the observations above. Induction of pregnancy to relieve arthritic symptoms is usually successful but social and

economic drawbacks make this an impractical therapy. There has been relief obtained in some cases by transfusion of blood of pregnant women but results are not at all beneficial in the majority of cases. Female sex hormones and oral administration of daily output of hormones in the urine of pregnant women have been tried, to no avail. Bile and bile salts, liver, liver extracts, cysteine, heparin, and blood transfusions from deeply jaundiced patients have proved of no value as a therapeutic measure. Some results (positive) have been obtained by producing jaundice by icterogenic serum or lactophenin. Notable articular remissions were produced in thirty-three of forty arthritic patients given icterogenic serum to produce jaundice but this procedure is not practical because the per cent of successful inoculations is small and there is such a long incubation period between inoculation and development of jaundice. Oral administration of lactophenin is somewhat more practical in producing jaundice. Hanssen, 1942, produced an effective bilirubinemia in four of seven arthritic volunteers, all of whom experienced remissions of their arthritis and Hench produced jaundice in three of nine arthritic volunteers.[8] In these cases the articular remissions were prompt but transient.

There are other diseases which are often relieved by pregnancy and jaundice so obviously this phenomenon of relief is not disease specific but it seems to be in a

closely allied group of disorders.

Listed below is a table of other diseases relieved by pregnancy and jaundice.

AMELIORATION BY PREGNANCY OR JAUNDICE

Conditions	Relieved by Pregnancy	Jaundice
Rheumatoid arthritis	*	*
Chronic arthritis with psoariasis (skin unrelieved)		*
Psoriatic arthritis (skin unrelieved)	*	**
Psoariasis (no arthritis)	**	
Intermittent hydrops, "true"	*	
Intermittent hydrops, symptomatic, with rheumatoid arthritis	*	
Fibrositis, primary	*	*
Asthma	**	**
Migraine	**	*
Hay fever	**	*
Addison's disease	**	
Myasthenia gravis	**	

* Encountered by Philip S. Hench.
** Cases reported by others.
Table reproduced from article by Hench.[8]

From this table, it might be assumed that there is a hormonal-biochemical disturbance in these disorders.

In addition to pregnancy and jaundice, there are other conditions which have given remissions of rheumatoid arthritis. Hench reports one of his cases who was a badly disabled rheumatoid patient. This patient had been given triple typhoid vaccine as a routine measure to induce fever and had responded promptly in remission of his

symptoms. This remission was sustained to a marked extent over a period of years for which no explanation was attempted.

Starvation, absolute or relative, has been tried occasionally to relieve rheumatoid arthritis and no conclusive results were drawn but there was some relief obtained in patients.

Surgery and anesthesia at times have given temporary relief. Slocumb used various anesthetics given to volunteers with rheumatoid arthritis and he obtained amelioration of symptoms in sixty per cent of cases for a short period of time (two to three days).

All of these various "accidental and experimental" methods seem to point to a common denominator that is etiologic in rheumatoid arthritis, and also tend to disregard the infectious theory of etiology. Stress seemed to play a part in producing the antirheumatic substance; there seemed to be an increase in this unknown substance during pregnancy, surgery, etc. With this in mind, it would appear logical that the adrenal cortex might be producing such substances, and in due course of time various compounds isolated from the adrenal cortex were tried, including compound E.

Kendall and associates, working on the adrenal cortex, isolated compound E. in 1935 and shortly thereafter Ingle showed that this compound had a marked effect on muscular activity.[11] A number of experiments were made

on mice and rats in regard to compound E but no therapy was attempted on humans for some years due to the scarcity of the compound and to the extreme difficulty in synthesizing even minute quantities of the crystalline substance. By cooperation between Kendall and other researchers, especially Dr. Sarett, compound E was synthesized for the first time in 1946, but not until late in 1948 had sufficient material been accumulated to provide enough for any clinical investigation.[3] In 1948 a much improved process for synthesis of compound E had been developed which yielded greater quantities of the crystalline compound.

INVESTIGATIVE THERAPY

In September, 1948, Hench and co-workers[6] used compound E for the first time on a patient with rheumatoid arthritis. The results were astounding in the relief of the rheumatic symptoms and physical findings of this patient. This initial case was a twenty-nine year old married female who had had severe rheumatoid arthritis for four and a half years, and who had responded poorly to many treatments. Her joints were stiff, swollen, tender, and painful on motion and x-ray studies revealed destructive changes in her right hip and in other joints to a lesser extent. Her sedimentation rate increased over a period of about two months from 75 to 109 mm. during which time lactophenin was administered orally in an unsuccessful attempt to produce jaundice in the patient. Compound E was given to

this patient September 21, 1948, by intragluteal injection of 100 mg. No apparent relief was noted for the first day and a half, after which time she could roll in bed with ease and her muscular soreness was decreased. She was able to walk with only a slight limp and with very little stiffness in three days after treatment was begun, which, just prior to treatment, was an impossibility. Her symptoms and signs were lessened daily until after eight days of 100 mg. per day the dosage was decreased to 50 mg. for four days and then 25 mg. for ten days. Rheumatoid symptoms increased and her sedimentation rate took a gradual steady climb from 86 to 100 mm. It was just by chance that 100 mg. was used for daily injection and not a lesser amount, but this chance may have been the spark that kept alive the investigative work, for, as proven in later cases, smaller quantities of compound E are ineffective in producing a remission of the disease in the majority of cases.

Since most of the literature on clinical investigation of compound E has come from Hench and co-workers at the Mayo Clinic, the statistics and cases will be for the greater part taken from the results of these men. Selection of patients was confined to those who had "moderately severe to severe" chronic polyarticular rheumatoid arthritis of four and one-half months to five years duration, all cases of which responded poorly to

previous therapy. Five patients were given compound E more or less continuously and nine patients given the substance from eight to sixty-one days; thus, both short term and long term administration and the results thereof could be studied intensively. In order to avoid over-enthusiasm in this treatment and in placing too much reliance on the patients' subjective improvement, charts were made for examination of joints and motion pictures were taken before, during, and after administration of compound E. Also numerous biochemical tests were made and recorded for each patient.

Control in these patients was accomplished in the Mayo Clinic series by use of an aqueous suspension of cholesterol indistinguishable from compound E in appearance. It was unknown to the patients when cholesterol and compound E were interchanged; it was also unknown for several weeks to three of the clinicians who were evaluating the therapeutic results. For this reason, there could be no unintentional falsification of evaluation either subjectively or objectively.

The first preparation of the compound used had larger crystals than the later preparations and probably caused delayed absorption. Compound E was used between September, 1948, and January, 1949, but after this E acetate was administered and the effects of the two preparations were essentially the same.

The general plan of dosage was 100 mg. of E on the first day and 300 mg. on the first day if E acetate was used, followed by 100 mg. per day thereafter. Smaller daily doses were found to be ineffective. Small doses several times per day seemed to affect the patients no differently than one large (100 mg.) dose per day. When the initial optimal improvement from this schedule of dosage was obtained, the daily dose was reduced to 75, 50, or 25 mg. in a few of the patients, in an attempt to find out if there was a smaller maintenance dose. However in these cases, sedimentation rates rose promptly and subjective and objective symptoms and signs were increased in severity. A minimum daily dose of 75 to 100 mg. appeared to be the maintenance dosage, but all of these patients were severe cases. Boland and Headley [1] reported results of three cases of mild to moderate arthritis which they treated with about one-half of the above-mentioned dosages. They used 50 mg. of compound E acetate daily for ten to fifteen days and thereafter 50 mg. every other day for twenty-one days. From this one can assume that the dosage has to be regulated according to individual cases as is seen with diabetes and practically all other diseases. If desirable effects are noted with a small dosage of compound E and just as long lasting results are obtained, obviously (because of expense and possible overdosage toxicity) it would be foolish to give large doses of the

compound. The remission of the disease in these three cases was not quite as dramatic as in cases treated with the larger amount of cortisone, but they did not raise their dosage to the most beneficial amount because this was a controlled study.

There is no doubt that "psychotherapy", bed rest, and hospitalization were factors in the improvement of these selected cases, but all other forms of therapy were discontinued several days before the administration of compound E.

The initial clinical effects observed were similar in all fourteen cases. Within a few days, muscle and joint function was greatly improved with reduction of stiffness, less aching and pain and tenderness. Muscular and articular stiffness diminished first, often within a day or two following the initial injection of compound E. Then followed decreased articular tenderness and pain on motion. Articular swellings diminished but there was a more varied effect than was produced in the above-mentioned effects. Sometimes this was slow and sometimes rapid. The ability to do common, everyday maneuvers, such as using the toilet or sitting and rising from chairs unassisted, climbing stairs, using hands for numerous small tasks, and so forth, was the thing that elated most of the patients. Besides these restored functions of muscles and joints, other effects were noticed: the appetites of the patients

greatly improved; weight gain was prevalent in most cases; a euphoria and sense of well being and increased mental capacity and decreased mental depression were all some of the other clinical effects noted. To these depressed, suffering patients, this therapy was like a miracle as long as the improvement of their condition was maintained.

Short term administration (eight to sixty-one days) was accomplished in nine of the fourteen patients and cholesterol replaced compound E. Symptoms began to return promptly within two to four days and the arthritis returned slowly in seven cases and rapidly in two cases. The sedimentation rates on the whole gradually rose to about the same as before treatment and occasionally to a higher level. There was a great variation in the time of temporary relief in these patients. For some relief was experienced for only a few days after compound E was discontinued and for others, the articular condition of the patient after treatment did not reach the severity at time of admittance in several months time. Also there were one or two in which there was a relapse into a more severe condition than had previously been seen. Therefore it is difficult to truly evaluate this type of therapy on such a small series of patients. In the "long term patients", four of the five were strikingly relieved as long as compound E was administered. The other patient

in this series of five received remission in the disease but had minor articular flare-ups on numerous occasions. She apparently developed a temporary endocrine disturbance from what was presumably due to prolonged use of the hormone. This patient experienced a cessation of menses, some acne, mild hirsutism, rounding of facial contours, and sudden weight gains and losses.

The following table will give an incomplete summary of the fourteen cases with some of the clinical and laboratory effects of compound E:

(Refer to Table on Page 14-A)

In Hench's series, several laboratory effects of compound E were recorded.

Sedimentation rates decreased markedly as is noted in the attached table. There was variation in these decreases though - some were prompt and some prolonged and in a few cases there was no decrease in the first three to nine days, even though there was exhibited good results in clinical improvement. The average decrease varied from 2 to 7 mm. per day until a steady low level was reached. The total decrease in sedimentation rates varied from 102 mm. to 17 mm. depending more or less on the height of the sedimentation rate before administration of compound E. An initial high sedimentation rate (over 100 mm.) in the majority of cases was found to be decreased by 50 to 75 per cent and in the initial low sedimentation rates the decrease averaged about the same. In all fourteen

Certain Clinical and Laboratory Effects of Compound E on Rheumatoid Arthritis

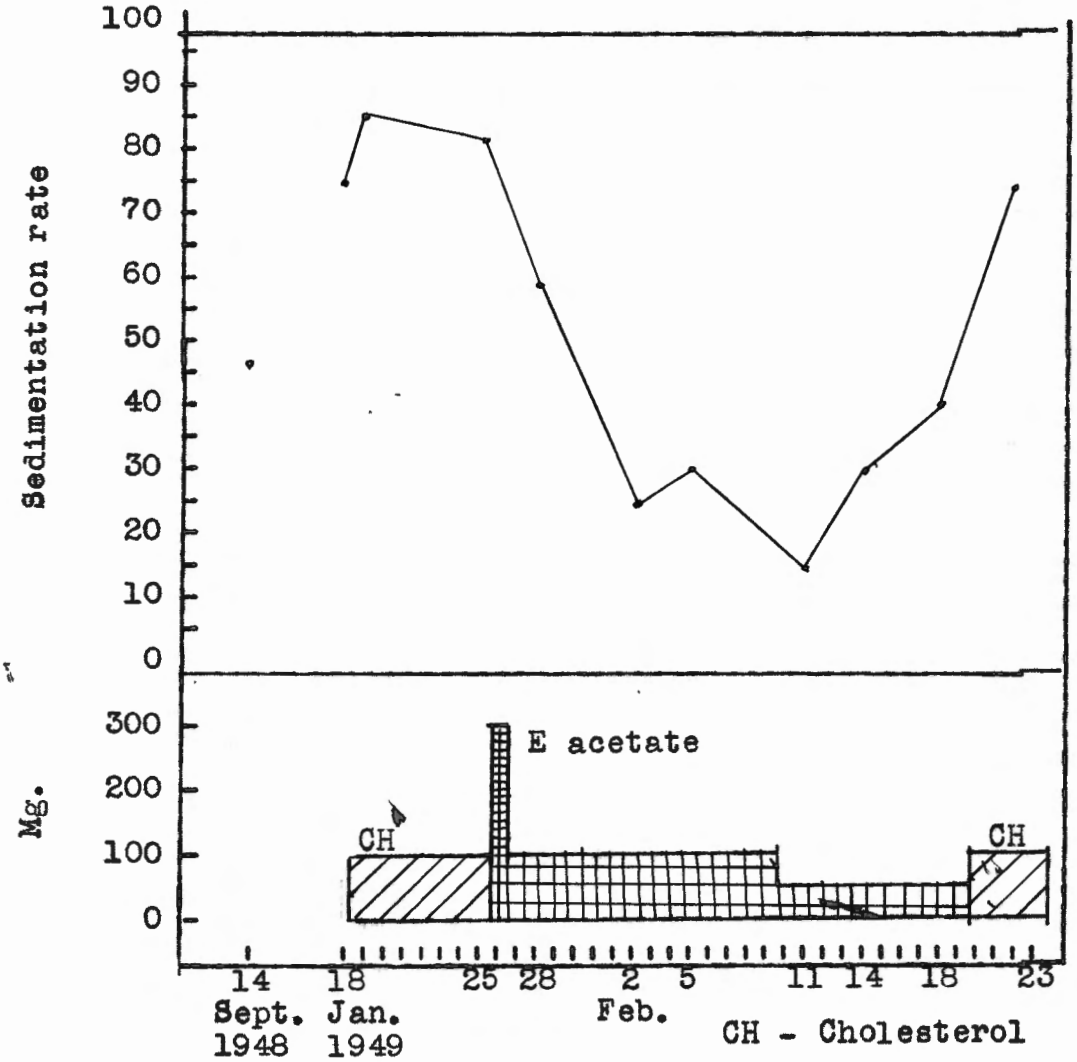
Case	Sex	Age	Chronic arthritis: Duration	Severity	Administration of compound E or E acetate, duration	Initial clinical improvement results; degree of	Sedimentation rates: Effect of hormone: rate reduced, mm. From	To	After	Incr. in rate, mm., after hormone discont.* To	After
1	F	29	4½ yr.	Severe	6 months	Marked	108	26	3 mo.	Use of	
2	M	41	5 yr.	Severe	1st pd.: 11 wk.	Marked	118	50	8 wk.	hormone just	
					2nd pd.: 3 mo.	Marked	114	59	11 wk.	discontinued	
3	M	64	3 yr.	Severe	1st pd.: 60 days	Marked	51	8	22 days		
					2nd pd.: 14 wk.	Marked	96	13	22 days		
4	M	41	2 yr.	Mod. sev.	1st pd.: 12 days	Marked	37	16	15 days		
					2nd pd.: 36 days	Marked	43	11	6 days		
5	M	34	4½ mo.	Very sev.	3 months	Very Marked	65	11	12 days		
6	F	49	3 yr.	Severe	10 days	Marked	47	14	10 days	70	12 days
7	F	53	2 yr.	Mod. sev.	24 days	Very Marked	103	14	30 days	58	11 days
8	M	62	5 mo.	Severe	9 days	Very Marked	50	10	9 days	38	8 days
9	F	44	2 yr.	Severe	25 days	Very Marked	81	17	17 days	76	5 days
10	M	49	5 mo.	Mod. sev.	61 days	Marked	115	13	35 days		
11	F	40	5 yr.	Mod. sev.	8 days	Very Marked	64	14	10 days	70	20 days
12	F	43	10 mo.	Mod. sev.	42 days	Marked	68	22	11 days		
13	F	31	4 yr.	Mod. sev.	30 days	Marked	71	13	26 days		
14	F	45	5 yr.	Mod. sev.	21 days	Marked	62	31	21 days		
15	M	29	3 yr.	Severe	‡						
16	M	49	10 mo.	Severe	‡						

* When rates in this column are not given, either the patient was still receiving compound E or its use had just been discontinued.

‡ Started April 3, 1949. Clinical results not mentioned in discussion.

Table reproduced from article by Hench and co-workers.[6]

cases there was not one single instance of sedimentation rates remaining the same, rising, or decreasing only slightly, before and after compound E was given. One other effect that was true in all cases was the rise in sedimentation rates after discontinuance of compound E, and this usually occurred within one to three weeks. A typical sedimentation rate graph is seen below.



Graph reproduced from article by Hench.[6]

In five severe arthritic cases, treated by Boland and Headley[1], the results in sedimentation rate rise and fall were essentially the same as noted by Hench, except in one case in which the sedimentation rate continued decreasing even lower after E acetate was discontinued. Likewise in three cases of mild and moderate rheumatoid arthritis the sedimentation rates fell and rose about the same as Hench's cases. In a very few cases the sedimentation rates of this total of twenty-two patients did not become normal but remained high even though much reduced from the upper limit.

Pre-existing abnormalities in serum globulin concentrations and serum albumin ratios tend to be corrected after a few days of treatment. In three acute rheumatic fever patients given compound E Hench and associates[7] reported a slight rise in serum albumin and a slight fall in serum globulin with a normalizing of albumin-globulin ratio in these cases.

Compound E was found to bring about a reduction in the 17-ketosteroids in the urine of a small percent but the urinary concentrations were in the low normal range before treatment. The corticosteroid excretion in the urine always increased when compound E was used.

Of the cases that Hench and associates and Boland and Headley were using compound E, about one-half were found to have a mild hypochromic anemia and in a few this

was moderate to severe. After treatment was begun, all of the cases with anemia showed a significant rise in hemoglobin and erythrocyte count, some very early and some after several weeks. The hemoglobin rise varied from .9 gm. to 2.4 gm. per 100 cc. and the increase in r.b.c. varied from 390,000 to 1,000,000 cells per cu. mm. Other effects on blood elements that have been discovered with the use of compound E are: marked immediate reduction in eosinophils, a lesser reduction in lymphocytes, and an increased total white count.

Dextrose tolerance tests were made on three patients in Boland's series[1], two of which were non-diabetic and one who was a diabetic. In one patient there was no significant change, in the second there was a slight reduction in tolerance, and in the diabetic rheumatoid patient, there was noted a temporary intensification of the diabetes which required three to five times the normal amount of insulin to control the diabetes. Upon discontinuation of cortisone in three days the insulin requirement was reduced to the original number of units. It is evident that caution must be used in administration of the extract to diabetics. Cortisone was not found to produce diabetes in the non-diabetic patient but ACTH has produced such. A number of experiments with test animals have been made regarding the role of compound E in glucose metabolism. Wells and Kendall [16,22,23]

found that the compounds of the adrenal cortex which have an oxygen on carbon 11 (A, B, E, F and G) have a specific antagonism to insulin. These compounds block out the inhibition of gluconeogenesis produced by insulin, which results in an accelerated rate of protein conversion to carbohydrate. Gratton and Jensen [4] in 1940 confirmed these findings in experimenting on mice and they came to the conclusion that the anti-insulin response produced by compound E is probably due to the ability of cortisone to promote the formation of liver glycogen. More thorough studies of Lewis [17] in 1940, Long [18] in 1942, and Kendall [13] in 1942, reveal that the gluconeogenesis probably for the most part does not come from body protein catabolism but from diverting amino acid radicals to pyruvic acid and glucose. At present, the exact role of compound E and the other "glycogenic" adrenal cortical extracts is not definitely understood but more than likely various hormones, including adrenocorticotropic hormone from the pituitary gland are interrelated in glucose metabolism.

In just one patient of the twenty-two cases reviewed was an articular biopsy made before and after use of the hormone. This knee specimen taken after use of compound E showed histological evidence of healing and much less inflammation than did the specimen from the same knee beforehand.

Toxicity and overdosage signs were not very remarkable but upon several occasions toxic symptoms did appear. An unnatural euphoria was exhibited by several patients but no conclusions could be drawn from this fact. At the Mayo Clinic, psychiatric studies were made on such patients, but thus far no data has been published on the findings. Boland, in one patient (previously mentioned) who had diabetes, noticed an increase in the severity of the diabetes and had to use much more insulin to control it. A mild insomnia was observed in several cases, but this was just for short periods of time. Occasionally transient pretibial edema was noticed, which disappeared with decreased dosage of the compound. Electrolyte and water balance studies have not been evaluated to date. It is evident that compound E produces hardly any of the toxicity that has been seen with use of ACTH, but until a survey of physiological and pharmacological effects is made over a long period of time and with a large series of cases, no conclusive statements can be made about toxic effects of compound E. It was noticed in one patient, who probably had had too long continuation of the hormone, a Cushing's syndrome in miniature, which was of a very temporary nature.

In addition to the use of compound E in treatment of rheumatoid arthritis, there are numerous other possible abnormal conditions which may respond favorably to this

hormone. Hench [7] obtained excellent results in treating three acute cases of rheumatic fever, using the dosage plan as mentioned earlier. In all three cases there was a rapid disappearance of the fever, tachycardia and polyarthritis and the sedimentation rates were speedily reduced. Even the abnormal electrocardiographic changes disappeared. Whether or not cardiac muscle and the valves of the heart were benefitted remained unknown and will for some time to come.

Heilman and Kendall [5] implanted lymphosarcoma in young mice and gave compound E to them. Rapid regression of the tumors took place in all the mice and completely disappeared in the female mice. Although these "cures" are dramatic, the tumors usually recur after a few days or weeks and then are refractory to treatment. The tumors influenced by compound E were of the lymphatic system as was also confirmed by Murphy and Sturm. [19] Heilman and Kendall thought the influence of compound E appeared to depend on stimulation of the rate of catabolism of proteins to a degree which resulted in death of the malignant cells. Further work with tumors and compound E can be expected and there may one day be some therapy devised to reduce such tumors or to even control them for a reasonable length of time in human beings. The results of these workers afford evidence that the lymphoid system is under some control of adrenocortical hormones.

Perera and co-workers[20] have given cortisone to two hypertensive patients and came to only one conclusion: "compound E exerted a depressor effect on the resting blood pressure of the hypertensive patients."

At present, very little information is available regarding compound E and gout but ACTH has given definite relief of this disease and this is supposedly because of stimulation of the adrenal cortex to produce more cortisone than normal. ACTH has been found to produce astonilhing favorable results in experimental therapy in a number of diseases such as; disseminated lupus erythematosis, periarteritis nodosum, chronic asthma, myasthenia gravis, alcoholic psychosis, acute nephritis, scleroderma, lymphomas, personality disorders and rheumatic fever and rheumatoid arthritis. Probably remission of these diseases in most cases was due to production of several hormones of the adrenal cortex through stimulation from ACTH administration, but cortisone may well be the responsible hormone in one or more of the above diseases. Much attention is being focused on ACTH, and the research done on this substance will undoubtedly clarify the role played by compound E, to a greater degree than seems to be the case to date.

SUMMARY

Cortisone has been given to 22 patients with rheumatoid arthritis, 19 of which had "moderately severe to severe" cases and 3 of which were mild to moderate. In every case there was a prompt remission of symptoms and signs and sedimentation rates dropped markedly and speedily. Upon taking the patients off of cortisone, the rheumatoid symptoms recurred, in most cases within several days to several weeks but in one of two cases the lasting effect had a duration of months. So far the side effects of the hormone are minimal and disappear immediately upon discontinuing therapy.

At present, no group of investigators has ventured an expression of theory that might explain the action of cortisone in treating rheumatoid arthritis.

Because of the small number of cases reported and the brief periods of administration of cortisone, definite conclusions cannot be drawn, but it might be postulated that cortisone is the naturally occurring anti-rheumatic substance, in view of the results obtained thus far.

With more cortisone and ACTH being made available each month and with the distribution of these substances disseminated among greater numbers of clinicians and researchers, there will be in the next few years

many questions answered regarding hormonal relationships in the production, diagnosis, and therapy of a number of diseases of mankind, but mainly the so called "collagen" diseases.

BIBLIOGRAPHY

1. Boland, E. W., and Headley, N. E.: Effects of Cortisone acetate on Rheumatoid Arthritis. J.A.M.A. 141: 301 (Oct. 1) 1949.

2. Cortical Hormones in Rh. Arth. Scope, No. 11, Vol. 2, 13-16, Oct. 1949.

3. Cortisone (Cpd. E), The Merck Report, July, 1949, 4-6.

4. Gratton, J. F. and Jensen, H. The Effect of the Pituitary Adrenocorticotropic Hormone and of Various Adrenal Cortical Principles on Insulin Hypoglycaemia and Liver Glycogen. J. Biol. Chem. 135: 511-517, Sept.,1940.

5. Heilman, F. R., and Kendall, E. C. The Influence of 11-Dehydro-17-Hydroxycorticosterone (Cpd. E) on the Growth of a Malignant Tumor in the Mouse. Endocrinology 34: 446-420, June, 1944.

6. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Cpd. E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis; preliminary report, Proc. Staff Meet., Mayo Clinic. 24: 181-197, April,13, 1949.

7. Hench, P. S., Slocumb, C. H., Barnes, A. R., Smith, H. L., Polley, H. F. and Kendall, E. C. The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Cpd. E) on the Acute Phase of Rheumatic Fever: Preliminary report, Proc. Staff Meet., Mayo Clinic. 24: 277-297, May 25, 1949.

8. Hench, Philip S. The Potential Reversibility of Rh. Arth. Proc. Staff Meet., Mayo Clinic. 24: 167-188 (March 30) 1949.

9. Holbrook, W. P.: Recent Advances in Management of Patients with Rh. Arth. New York Med. 4: 7-12 (April 5) 1948.

10. Ingle, D. J., The Production of Glycosuria in the Normal Rat by Means of 17-Hydroxy-11-Dehydrocorticosterone, Endocr. 29: 649-652 (Oct.), 1941.

11. Ingle, D. J., and Kendall, E. C., Influence of Amorpheus Fraction from Adrenal Cortex on Efficiency of Muscle. Proc. Soc. Exper. Biol. and Med. 45: 602-606 (Nov.) 1940.

12. Ingle, D. J., and Thorn, G. W. A comparison of the Effects of 11-desoxy corticosterone acetate and 17-Hydroxy-11-Dehydrocorticosterone in Partially Depancreatized Rats. Am. J. Physiol. 132: 670-678, April 1941.

13. Kendall, E. C. Hormones of the Adrenal Cortex. Endocrinology 30: 853-860, June 1942.

14. Kendall, E. C. Some Observations on the Hormone of the Adrenal Cortex Designated Cpd. E. Proc. Staff Meet., Mayo Clinic 24: 298-301 (May) 1949.

15. Kendall, E. C. The Adrenal Cortex. Arch. Path. 32: 474-501, Sept., 1941.

16. Kendall, E. C. The Function of the Adrenal Cortex. Proc. Staff Meet., Mayo Clinic 15: 297-304 May 8, 1940.

17. Lewis, R. A., Kuhlman, D.,Delboe, C., Koepf, G.F., and Thorn, G. W. The Effect of the Adrenal Cortex on Carbohydrate Metabolism, Endocrinology 27: 971-982, Dec., 1940.

18. Long, C. N. H., A Discussion of the Mechanism of Action of Adrenal Cortical Hormones on Carbohydrate and Protein Metabolism, Endocrinology 30: 870-883, June, 1942.

19. Murphy, J. B., and Sturm, E., The Effect of Adrenal Cortical and Pituitary Adrenotropic Hormones on Transplanted Leukemia in Rats, Science 99: 303, April 14, 1944.

20. Perera, G. A., Pines, K. L., Hamilton, H. B., and Vislocky, K., Clinical studies of 11-Dehydro-17-Hydroxy Corticosterone in Hypertension, Addison's Disease and Diabetes, Program, Forty-first Annual Meet., Am. Soc. Clin. Investigation, May 2, 1949 pp. 41-42.

21. Selye, H. The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. 6: 117-230, Feb. 1946.

22. Wells, B.B. The Influence of Crystalline Compounds Secreted From the Adrenal Cortex on Gluconeogenesis, Proc. Staff Meet., Mayo Clinic 15: 294-297, May 8, 1940.

23. Wells, B. B., and Kendall, E. C., The Influence of the Adrenal Cortex in Phlorazin Diabetes, Proc. Staff Meet., Mayo Clinic 15: 565-573, Sept. 4, 1940.

24. Wells, B. B. and Kendall, E.C. The Influence of Corticosterone and C 17-Hydroxy Dehydrocorticosterone (Compound E) on Somatic Growth, Proc. Staff Meet., Mayo Clinic 15: 324-328, May 22, 1940.