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Effect of cortisone on the erythrocytic sedimentation rate in rheumatoid arthritis

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THE EFFECT OF CORTISONE ON THE ERYTHROCYTIC SEDIMENTATION RATE IN RHEUMATOID ARTHRITIS

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Arthritis is one of our oldest and most neglected diseases. The earliest known example of multiple arthritis in a fossil vertebrate is in a skelton of a platecarpus (a large swimming reptile) which lived about 100,000,000 years ago. Chronic arthritis of the spine was present in the ape man of 2,000,000 years ago as well as in our ancestors, the Java and Lansing men of 500,000 years ago and Egyptian mummies dating to 8,000 B.C. The Romans built extensive baths through out their empire because of this disease.

Rheumatic diseases are the commonest cause of chronic illness in this country and rank second in causing temporary and permanent disability. It has been estimated that nearly 7,000,000 people (at least one in every twenty persons) in the United States have some form of rheumatic disease. Arthritis surpasses injury from accidents from the standpoint of days lost from work. The rheumatic diseases disable ten times as many persons per year as does diabetes or tuberculosis and seven times as many persons as cancer. Among chronic diseases rheumatism cripples in the largest number and kills in the smallest. Because of its ability to cripple without killing, it should be put at the head of all other chronic diseases as of

preeminent medical, economic and social importance. (1)

It has now been accepted that rheumatoid arthritis is a generalized disease with definite constitutional manifestations. None of the many theories of etiology (endocrine, infectious, metabolic, neurogenic or circulatory) has been generally accepted.

Because of the terrific import which Cortisone initially has had in the therapy of rheumatoid arthritis, this writer has endeavored to review the pert-inent literature concerned with one aspect—what effects, if any, has this new wonder drug, Cortisone, on the erythrocytic sedimentation rate in rheumatoid arthritis? A critical evaluation of the value of this laboratory procedure as an indicator or index of Cortisone affect on the inflammatory activity in this disease process

is attempted. For many years this laboratory procedure has been generally accepted as one of the most reliable indicators, in most cases of rheumatoid arthritis, as to the degree of disease activity present. Then too this question must be answered - can the results of this procedure, after Cortisone therapy, be accepted as a true indicator of disease improvement or must the clinician rely on other methods available to him?

Speaking before the Heberdeen Society in London

in October 1948, Dr. Philip Hench of Mayo Clinic first reveal d his theory of the potential reversibility of rheumatoid arthritis. (2) "Rheumatoid arthritis has two sharply contrasting characterisitics, that of potential chronicity and that of potential reversibility. So graphically ha- the chronic progressive form of this disease been de-cribed that it has become almost indelibly impressed on the minds of physicians and laymen alike as the archetype, not only of rheumatoid arthritis, but of all the arthritides. The contrasting characteristic of rheumatoid=its potential reversibility had not been sufficiently described or appreciated but to the clinical investigator, it is much more important than its potential chronicity. Of much more interest and more dramatic than the fe ble remissions induced by foreign protein reactions, starvation, or surgery, or even the sturdier remissions induced by chrysotherapy, are those which he noted to arise accidentally, appearing in connection with coincidental pregnancy or hepatitis with jaundice. These two conditions were usually potent antagonists to rheumatoid arthritis. In the presence of either one, rheumatoid arthritis found it difficult to progress or to do more than retr at. Thus any theory on the

etiology must necessarily take into account the powerful ameliorative influence of jaundice and pregnancy". It thus became easier for him to consider that rheumatoid arthritis represented not a microbic disease, but a basic bioch mical disturbance of an unknown type which is accid ntally and transiently corrected by some incidental biologic changes common to a number of apparently unrelated events, most notable of which were pregnancy and jaundice. Obviously there existed a great unrealized potential for the relief of rheumatoid arthritis, a potential which he realized must be brought to reality.

It was finally conjectured to Hench and others that the hypothetic common demominator of "anti-rheumatic substance X" was not a disent gration product from a damaged liver, but was probably a biologic compound specific in nature and function, a compound which was normal to th human organism. After consideration of numerous chemical compounds, it was conjectured that the "anti rheumatic substance X" might be an adrenal hormone. In 1941, Hench and his cohorts recorded their interest in adrenal cortical fractions in general and Kendall's compound E first isolated in 1935 and identified in 1938 in particular. But since

Compound E was not available until September 1948 and was thus not available to be used for experimental purposes until then, a considerable length of time had elapsed until the compound could be used for clinical purposes to note its effects.

If we are to understand the work done on Cortisone we must study the present day work on the adrenal steroids. To 1950 28 steroids had been isolated, but only 6 of t em are active as far as known. (3) These six steroids can be divided into three groups. The first group contains only desoxycorticosterone and the second contains corticosterone, 17-hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone. You will see that these are oxygenated at the 11 position and because of this are called oxysteroids. It is this group with which we are chiefly concerned because it contains compound E or Cortisone. Group three contains compound S. As early as 1930 Button (4) enunciated the theory that the "prepotent function" of the adrenal cortex was to regulate carbohydrate metabolism. He observed that when adrenalectomized animals develop acute hypoglycemia and low glycogen levels and that when mormal fasted animals were given large doses of cortical extracts there was an increase

in the blood sugar level and in both liver and muscle glysogen. In 1936 Mason, Myers and Kendall (5) and in 1937, de Fremery and his co workers isolated compound B (Corticosterone) and dehydrocorticosterone now called compound A, both extracts of the adrenal cortex, in crystalline forms. Kendall (6) (1935) at Mayo Clinic first isolated 17-hydroxy-11-dehydrocorticosterone from the adrenal cortex and called it compound E.

In the several methods available for sedimentation rate determination, there is general agreement regarding the principles involved. The phenomenon is primarily dependent on the properties of the plasma and consists of three phases. (7) The first is a period of aggregation of the red cells, generally accepted as consisting of roulaux formation. This is followed by a period of constant settling velocity which is believed to be dependent primarily on the size of red cell aggregates. After a variable length of time, the rate of settling slows gradually as the cells become packed together at the bottom of the tube. This "packing phase" is influenced by the volume of packed erythrocytes. To eliminate this influence the Rourke Ernstene (8) and Cutler (9) methods actually

determine the settling velocity during the period of constant settling so the packing phase is not included by these procedures. The Wintrob method does not include the packing phase and attempts to correct for it on the basis of hematocrite readings. (10) In the Westergren technique, the length of the tub used (200 mm.) and the standard dilution with citrate minimized the packing effect and no correction is usually applied. (11) Hal and Curtis (12) in a comparative study found this to be justified, as they demonstrate that the one hour reading with this technique was directly proportional to the settling velocity during the period of constant fall.

However, the volume of erythrocytes can also affect the velocity during the period of constant fall. This is apparently due to an upward displacement current in the fluid medium, through which the cells are settling. This upward displacement will be increased by an increased volume of erythrocytes, with resultant slowing of the apparent sedimentation rate. This necessitates correction in the Rourke Ernstene Method (8) and is included in the correction used with Wintrob Method. (10) Hal and Curtis (12) believe that in the Westergren Method, the increased height of the

blood column results in less retarding effects from these displacement currents.

In the Wintrobe (11) and Rourke-Ernstene (8) methods correction for hematocrite readings are made on charts derived from the determination made by removing or adding plasma to the blood sample. The validity of this concept has been severely criticized by Cutler et al, (9) who have shown the manipulation will alter the degree and incidence of Rouleaux formation. Alteration in size and shape of the red blood cells also affect the sedimentation rate, apparently by inhibiting or augmenting the tendency toward Rouleaux formation.

In essence the sedimentation rate is an empiric determination, the value of which has been established by clinical experience. It correlates roughly better with the level of plasma fibrinogen than with any other factors which have been measured, although it is influenced by the levels of other plasma protein components. It is also influenced by the packed red cell volume and in general the results can relate better with clinical status if this influence can be minimized or corrected. (13)

Hench and his co workers (14) first administered

Cortisone (Compound E) to fourteen patients with sev re or mod rately sev re rheumatoid arthritis in 1948 when enough of th drug was availabl for clinical trial. Changes produced in the sedimentation rat s were noted. In every case, when this drug, compound E or its acetate, was employed, sedimentation rates (Westergren) decr ased markedly, sometim s promptly and rapidly, sometimes more slowly. In a few cas s the rate was refractory the first thre to nine days despite marked clinical improvement. Sedimentation rates usually decr ased at the moderate speed of 2 to 4 mm. daily average; in other cases rapidly at a daily average of 4 to 7 mm., occasionally at the very rapid rate of more than 7 mm. daily. Rates of decrease varied from patient to patient, and were influence by the dose of different preparations of compound E. Most rates became normal within 10 to 35 days but rates, although much reduced, did not become normal in 3 cases.

Boland and Headley (1949) (15) selected 8 patients to note the effect of this n w therapeutic agents, Cortisone, on their rheumatoid arthritis. 5 of the patients had the disease in a severe and decidely active stage and 3 patients were less severely aff cted with the disease. Each of the 5 with severe arthritis had multiple

involvement of multiple peripheral joints and great disability; 2 had involvements of the spine also. The duration of the disease varied from 4 to 14 years. Sedimentation rates before the use of Cortisone were (in order of cases) 74, 128, 70, 97 and 80 mm. in one hour. (Westergren method.) Cortisone acetate was administered to each patient for 8 days. Daily dosage was guided by the experiences of Hench, Kendall, Slocumb and Polley. (14) 4 of the 5 patients received an initial dose of 300 mgm. given intramuscularly on the first day and 100 mgm. daily thereafter for 7 days. One patient (case 3) received 200 mgm. on the first and second days and 100 mgm. thereafter for 6 days. Sedimentation rates decreased significantly in each of the 5 cases; decreases varied from 15 to 75 mm. within 8 days. The degree of clinical improvement was not necessarily reflected by the reduction in sedimentation rates. Sedimentation rates after 8 days of Cortisone administration were (in order of cases) 49, 53, 34, 56, 59. However, 2 months after Cortisone withdrawl, sedimentation rates (in order of cases) 79, 44, 74, 78, 77 mm. per hour by the Westergren method. 2 patients with moderate and 1 patient with mild but definite rheumatoid arthritis were given 50 mgm. of Cortisone

daily for 10 to 15 days until the clinical manifestations had subsided almost completely. The sedimentation rate in case 1 was reduced from a pre Cortisone level of 35 mm./hr. to 11 mm./hr. on the 10th day. Case 2 showed a decrease from 44 mm. prior to Cortisone administration to 12 mm./hr. after 15 days of therapy. Case 3 showed a reduction from 26 mm./hr. to 6 mm./hr. by the 12th day. (Westergren method.)

Within a short time after the first reports by Hench and his co workers (14) were published, O'Connell and Burns (15) working in Rhode Island tried Cortisone therapy on 2 patients afflicted with rheumatoid arthritis. The first patient was a 36 yr. old female who had suffered from the disease for 10 years. Laboratory data at the time of admission showed her sedimentation rate to be 24 mm./hr. Cortisone therapy was started February 4, 1950 with an initial injection of 250 mgm. intramuscularly. For an initial period of 10 weeks, 100 mgm. was given daily. Two months after beginning of therapy the E.S.R. had fallen progressively to the level of Cutler 6 and Wintrobe 0 mm./hr. in July 1950. Similar results were noted in the second patient. In this case, the sedimentation rate was reduced

comparably after 21 doses of Cortisone in 24 days. It was the authors opinion that good results with marked clinical improvement as well as improvement determined by the E.S.R. were obtained. However, this series was limited and the author felt further evaluation of the clinical usefulness of this drug as a theraputic aid in rheumatoid arthritis must await results of further investigation in a larger series of patients.

Utilizing the most exhaustive of studies to determine the physiological effects of A.C.T.H. and Cortisone as well as the clinical usefulness of these steroids in the modification of pathological processes, Thorn, Forsham and Frawley (16) noted that the effect of Cortisone on the eosinophilis sedmentation rate in rheumatoid arthritis consists essentially of little response during the early days of treatment in spite of good cli ical response, but generally falls to normal or near normal levels within 1 or 2 weeks of therapy.

From a large group of patients with rheumatoid arthritis, 8 patients wer selected arbitrarily by Spies and De Magyer (17) for a study of the effects of 7 different steroid compounds as well as Cortisone on the arthritic processes. All patients were

excluded that gave a history of mild arthritic involvement or who had only mild evidence of the disease. Also excluded wer all cases which were so far advanced that they had ankylosis of the joints. Each patient selected for the study fulfilled the criteria: an elevated E.S.R.; physical handicap to a point where he could not function without the assistance of others; swollen and painful joints; a distaste for food; loss in body weight, swollen, painful and tender joints, and some anemia. In each of the 8 cas s th author tried 7 different st roid compounds; pregnene, pregnon , 17-methyl-delta-5-androstendiol 3, 17-hydroxyprogesterme, 17-alpha-hydroxy-11-desoxycorticost rone-21-acetate, desoxycorticosterone acetate and ergostanyl acetate successively without any evidence of the patient receiving any ameliorating effects or any objective improvement being noted. Cortisone acetate was then administrated subsequently to 4 of the 8 patients. Chol sterol suspensions were injected intramuscularly in the other 4 patients as a control. In each of the 4 cases treated with Cortisone, a significant decrease in the sediment-ation rates was noted as well as clinical improve-

ment being quite good.

Among the first workers in England to note the clinical effects of Cortisone in rheumatoid arthritis were Copeman, Savage and Bishop. (18) In the latter part of 1950, they subjected 5 pati nts, who had suffered from polyarthritis of the rheumatoid type for more than 6 months, to Cortisone. The experiments were controlled by means of a ch lesterol compound which was injected. The dosage schedule consisted of 300 mg. the first day, 200 mg. the second and 100 mg. daily for the following 8 days. In all the case« the E.S.R. fell significantly during the trials. Exemplary of the results was case 1, a married woman, age 49, who had suffered from rheumatoid arthritis for 1⅛ years. Joint motion was markedly limited and codeine was necessary for control of pain. Sedimentation rates were repeatedly found to li between 50 and 60 mm/hr. (Westergren.) The response to Cortisone was dramatic. By the third day of therapy, the patient could dress unaided. One month later, the residual improvement was considered to be about half as much as she had attained during the course of Cortisone therapy although the E.S.R. had risen

to 54 mm./hr within a week of discontinuence of the injections.

From a large group of patients with rheumatoid arthritis who had been under observation at the nutrition clinic, Hillman Hospital, Birmingham, Ala., Stone and Spies (19) selected 4 men and 3 women. All were patients with mild arthritis or those who had ankylosis of the weight bearing joints or the joints of the hands and fingers. Every case showed a significant decrease in the E.S.R. within 2 to 15 days. Dosages of Cortisone varied from 325 to 1650 milligrams.

Dr. Edward Rosenberg (20) in experiments conducted at Michael Reese Hospital, Chicago, from April, 1949 to January, 1951, confirmed the observations of Hench, Kendall, Slocumb and Polley. (2) Administration of Cortisone to patients with rheumatoid arthritis invariably resulted in relief of the arthritis. High sedimentation rates returned toward normal and inverted albumin globulin ratios returned to normal. The graphs shown below show the effects noted by Rosenberg during the prolonged administration of Cortisone. It is noted that the initial sedimentation rate fell rapidly following the initiation of Cortisone therapy. A rest

period durin· the early we ks of February was accompanied by a moderate rise in sedimentation rate and partial return of symptoms. When doses of Cortisone were resumed symptoms improved. When doses were reduced to 50 mg. the sedimentation rate rose and symptoms were more marked.

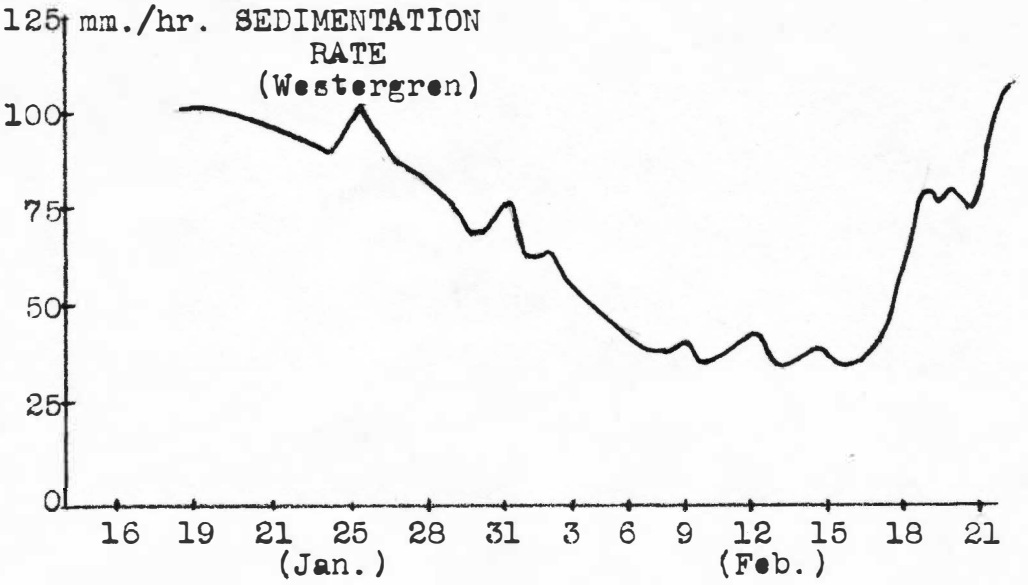

Fig. 1.

Immediate effect of Cortsone on sedimentation rate in rheumatoid arthritis.

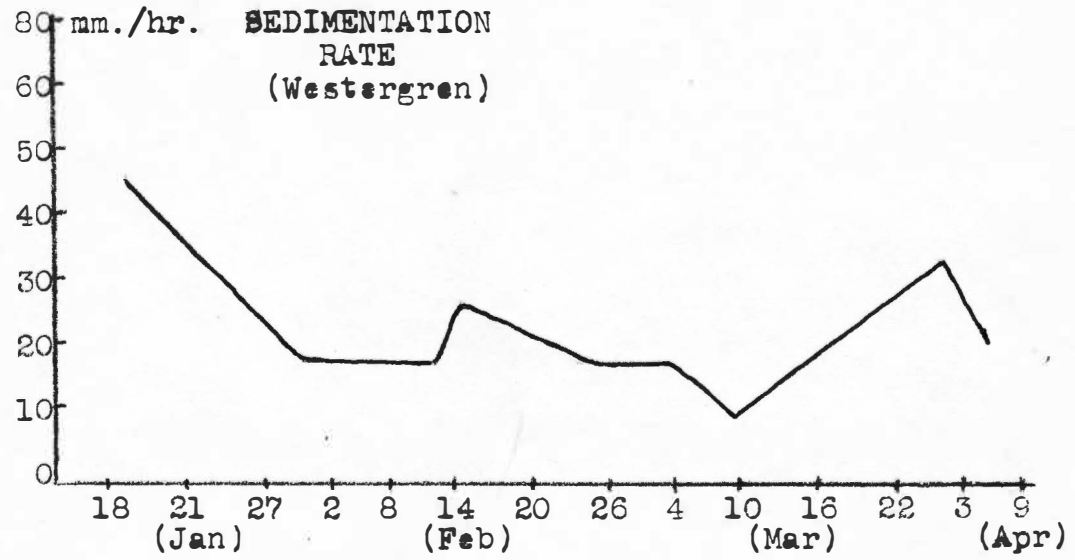

Fig. 2.

Effects during long term administration of Cortisone in rheumatoid arthritis.

Bunim (21) in studies conducted in New York noted the laboratory response induced by Cortisone in rheumatoid arthritis. All cases showed significant decceases in sedimentation rates within 10 days after initiation of therapy with Cortisone. Relapse within a few weeks after Cortisone was discontinued was the rule.

In an attempt to compare the response of rheumatoid arthritis to different methods of management, Freyberg, Adams, Durivage and Traeger (22) utilized 3 different modes of therapeutic management. These methods were: (a) administration of Cortisone in short courses separated by rest periods; (b) sustaining the benefits of this hormone by other forms of treatment so that Cortisone did not have to be repeated for long periods; (c) developing an effective method for prolonged use of Cortisone without harmful results.

Basic conclusions reached by these authors after utilization of the 3 different methods of management in 31 selected cases of rheumatoid arthritis were: that in the interval type of management with Cortisone, (17 patients) the disease improved to a great degree, the sedimentation rates usually became normal and that after the drug was stopped, a prompt relapse

resulted which responded promptly to reinstitution of Cortisone. Efforts to sustain by other drugs failed (9 patients). Long term therapy usually gave good results with E.S.R. and clinical manifestations roughly paralleling each other.

Using as case material patients treated in the Arthritis Clinic, University of Minnesota and in the private practice of Bilka, (22) a total of 36 cases of rheumatoid arthritis were studied; 26 of which were classified as of the severe type. Parenteral Cortisone, given intramuscularly in daily injections was used in 21 cases. Oral Cortisone was used in 15 cases. Patients were given 150 to 200 mg. of Cortisone for the first day or two, after which the dose was reduced to 100 mg. per day. Total doses ranged rom 8 gm. to 9.975 gm. with mose patients receiving 2 to 3 gms. Period of administration was from 1 week to over 5 months. Practically in all cases so treated, the authors noted a dramatic response to Cortisone with a marked reduction in E.S.R. As is generally noted the symptomatology of the rheumatoid arthritis closely paralleled the fall in E.S.R. which took place in all of the cases treated.

Early in 1951 Norcross, Lorkie and Talbott (23) determined to evaluate certain steroids including Cortisone in affecting the course of rheumatoid arthritis. 24 out of 67 patients afflicted with this disease were meticulously studied after Cortisone therapy. All 24 of the patients so treated exhibited significant improvement with this type of therapy. 5 patients had a temporary complete remission in the course of the rheumatoid process, and 15 others had marked objective and subjective improvement. During Cortisone therapy, the sedimentation rate became normal in 8 persons and was significantly reduced in 8 others.

Swedish workers, Berglund; Nordensen and Olhagen (24) were primarily interested in determination of serological reactions following Cortisone therapy in rheumatoid arthritis when they studied 2 such cases. It was noted that both cases which had eosinophilic sedimination rates of 120 to 130 mm/hr. before therapy showed dramatic response clinically and within 3 to 4 weeks exhibited E.S.R. of 15 mm./hr. or less. Upon the cessation of Cortisone therapy the E.S.R. rose rapidly to pre-therapy levels or higher in 2 weeks or less.

Writing in June, 1951, Dr. R. J. Tivort of England (25) relatss his experiences with a case of rheumatoid arthritis which had been successfully treated with Cortisone for 8 months. The boy, age 15 years, was diagnosed as suffering from the disease in April of 1950. His esinophilic sedimenation rate was raised to 90 mm./hr. (Westergren) Failurs of gold salt therapy after 6 injections at weekly intervals was noted. At th. beginning of Cortisone therapy, his E.S.R. was 50 mm./hr. The usual initial dosage values for Cortisone were employed and dramatic response was noted in 2 weeks. The E.S.R. fell to 14 mm./hr. The dosage was gradually reduced to 50 mg. daily, thence to alternate days, twice weekly, weekly, and then every 2 weeks. The E.S.R. had remained normal on the 50 mg. dosage every 2 weeks and excellent progress continued. Tivort was thus convinced that low dosage was of considerable value in th th rapy of the milder type of rheumatoid involvement and if sustained, with necessary alt ration to me t changing physiological demands, was of considerable value in the therapy of this disease.

During the past year ar the John Gaston Ho pital in Memphis, Tennessee, 6 cases suffering from chronic rheumatoid arthritis were treated with Cortison by Dr. Fred Tatum. (26) The average dosage, (Cortison) per pati nt was 3.5 gm., the average duration of administration being 37 days. Sedimentation rates which previous to th rapy were quite high decreased rapidly to normal. The author necessarily reserved judgement of value of the steroid as a treatment of the disease because of his own limited experience, but did feel that further study would prove the steroid compound to be a valuable, theraputic aid although not a cure for the disease process.

Lefkovits and Schupbach (27) were primarily int rested in comparing the effects of Artisone Acetate and Cortisone on rheumatoid arthritis. 9 selected patients from Kennedy Veterans' Hospital, Memphis, were chosen for t studies. The duration of the disease varied from 18 months to 29 years. 100 to 200 mg. of Artisone was given twice daily for a period of 4 to 40 days during which complete physical and chemical studies of the patients were made. A controlled study of 1 to 31 weeks was made and none of the 9 patients exhibited an subjective or objective

improvement. Blood E.S.R. were essentially unaff cted by the Artisone therapy. Subsequently 3 of the 9 patients were chosen by the investigators to undergo Cortisone therapy. Dosage schedules were arranged so that the lowest effective therapeutic dosage could be used. All 3 of these patients experienced subjective and objective improvement, blood eosinophilic rates dropping from 39, 42, and 34 mm./hr. respectively previous to Corti one therapy to levels of 16, 21 and 15 mm./hr. respectiv ly after therapy. Thus the value of Cortisone in cases of rheumatoid arthritis refractory to the action of steroids similar to Cortisone was proved by these investigators.

Steinbrocker and his group (28) presented a report of their experiences with Cortisone as A.C.T.H. therapy in 72 cases of rheumatoid arthritis. Standard dosage patterns of Cortisone were employed according to the severity of the individual case. Cholesterol controls were employed. Results are tabulated below. (Fig. 3)

Figure 3

Results of Administration of A.C.T,H. and Cortisone in Rheumatoid Arthritis.

No. of Cases	Complete Remission	Greatly Improved	Slightly Improved	No. Impr. or worse
72	3 / 4 %	29 / 40 %	39 / 54 %	1 / 2 %

Initial Short Term Hospital, 10 to 30 days

Ambulatory Maintenance 3o to 34o days later

55

Response as noted clinically correlated quite closely with corresponding changes in the sedimentation rates.

Price, Lightbody, Reveno, and Heide (29) included a total of 63 cases in their reports, all of which had received Cortisone for at least three months. The group consisted of 26 males and 37 females ranging in age from 19 to 70 years. All had multiple joint involvement with the duration of illness varying from 4 months to 36 years. Except in a few cases, the dosage of Cortisone administered consisted of an initial intramuscular injection of 300 mgm. of Cortisone followed therafter by 100 mgm. daily for

two weeks. After this the do-age was reduced to 100 m m. on alternate days from 1 to 3 weeks. Thereafter, the attempt was made to maintain the patient on 150 mgm. twice weekly. Many, however, required more frequent injections. Sedimentation rates (Westergren) were determined in practically all patients immediately before the beginning of Cortisone therapy, and follow up determinations were then made after 2 weeks, and in some, at later intervals during the administration of the steroid. The largest number of patients, 17, had initial values which were moderately elevated (30 to 40 mm./hr.) ; 11 showed extreme activity with a fall of 60 mm./hr. or more, and the remain ing fell between these two extremes. Following two or more weeks of Cortisone therapy, 8 patients showed no appreciable change, 11 exhibited a significant increase, while 27 showed a very significant decrease in the eosinophilic s dimenta-tion rate.

In contrast to the completely negative results obtained by the use of d soxycorticost rone acetate with ascorbic acid and Delta-5-Pregnenolon in the therapy of rheumatoid arthritis, Wingfield, Toone,

Williams and Becker (30) reported on 10 cases of rheumatoid arthritis treated with Cortisone during 1951. Standard accept d dosage schedules as used by the majority of therapists were employ d. 2 of the 10 patients showed excellent results with relief of resting pain, and joint and muscle stiffn ss. Joint swelling and deformities were controlled well. Sedimentation rates dropped from levels of 50 mm./hr. to 30 and 47 mm./hr. respectively after 15 weeks of therapy. Case 2 showed a drop in sedimentation rate to 23 mm./hr. aft r 3 weeks of therapy but again rose to the 15 week level of 47 mm./hr. 4 cases showed good results, 2 cases, fair results; and 2 cases poor results both clinically and objectively as noted by failure of depression of the sedimentation rates.

Some clinical results published by Bagnall (31) in August of 1951 threw a new light upon the subject of the effect of Cortisone thsrapy on sedimentation rates. He warns in his papsr against the too great a belief in the reliability of the sedimentation rates in patients receiving Cortisone therapy. In his data prssentsd, it appears that when Cortisone is administered orally, the fall in E.S.R. not infrequently outstrips the clinical rssponse and may

even lull the physician into a false state of security. By contrast, when Cortisone was injected intramuscularly, the clinical improvement may occur long before the fall in E.S.R. He states that even a substantial rise in E.S.R. may occur or the fall in E.S.R. may be so long delayed as to suggest that Cortisone is of no benefit if the clinical evidence of improvement is overlooked. Using Cortisone therapy on 43 cases of active rheumatoid arthritis, the E.S.R. was estimated twice weekly by the standard Westergren technique. 100 mgm. was the standard daily dosage given by 1 injection parenterally or in 4 25 mgm. doses by mouth. He found that in many cases, there is often a paradoxical behavior of the sedimentation rate after Cortisone therapy. If he employed the parent ral method of administration of Cortisone, there was a tendency for the E.S.R. to lag behind clinical improvement. When the oral method of administration was employed, however, there is a tendency for the E.S.R. to fall prior to the time when maximum clinical improvement was observable. Despite this, in at l ast one third of the patients receiving Cortisone by either route, there was a parallel fall in E.S.R. corresponding to the rate and degree of clinical improvement. In

patients with a normal E.S.R. prior to Cortisone thsrapy, there is no rise in the E.S.R. even though the parentsral method of administration is employed. With either method of administration, he occasionally encountered patients who responded adversely to Cortisone. This rare advsrse response appeared to start early with parentsral Cortisone therapy and was accompani d by a parallel rise in the E.S.R. With oral Cortisone, in the one instance he observsd, it occurred late after an early satisfactory remission and the E.S.R. remained normal until Cortisone was stopped.

Dr. William Wolfson (32) of the Michael Reese Rheumatoid Arthritic Research Group, in speaking b fore the First Clinical A.C.T.H. Conference, revealed that his ressarch group had be n greatly interested in the correlation of clinical improvement, decrease in sedimentation rate, and regression of abnormal s rum protein changes during remissions induced by Cortisone because of the possibility that such correlations might point toward the mechanism of action of these substances. Observations were made during administration of Cortisone, Westergren and Wintrobe sedimentation rates being followed and frequent serum protein

fractions determination performed by a chemical method which gives results comparable to el ctrophoretic analysis. The typical abnormalities present before Cortisone administration were elevated sedimentation rates, low serum albumin concentrations, high serum alpha globulin concentrations and high serum gamma globulin concentrations. In the regression of these findings when Cortisone was given, the first change noted was an increase in the ratio of serum albumin to serum globulin. They noted that clinical improvement and improvement in serum protein were much more closely associated than clinical improvement and decrease in sedimentation rate. The impression was gained from the study of Cortisone induced remissions that the elevated sedimentation rate appears to be a much more sensitive and persistent indicator of disease activity than is any abnormality in the serum protein fractionation pattern. Apparent clinical well being and normal serum protein patterns could, in fact, coexist with sedimentation rates as high as those present before treatment. On the other hand, the finding of serum protein patterns which were returning to normal may give objective evidence of increasing control of disease activity long b fore this fact could

have been established by study of the sedimentation rate.

One of the most interesting and informative pieces of research concerning this problem of Cortisone effect on sedimentation rate is the work of Vaughan, Bayler and Favour (33). They correlated the gamma globulin and fibrinogen levels with the E.S.R. in the blood of patients with active rheumatoid arthritis who were receiving Cortisone as a therapeutic agent. The authors found that these hormones depress the level of both gamma globulin and fibrinogen in the blood. These investigators believe that the changes in concentration of the two proteins were sufficient to cause the alteration in sedimentation rates following hormone therapy. They suggest that the sedimentation rate might be used as the eosinophilic count is used, as an index of continued hormonal activity and not as a criterion of the effectiveness of the hormone in reducing disease activity.

SUMMARY

The accession of Cortisone as a therapeutic agent in rheumatoid arthritis has had a profound effect on the rationale of th rapy in this disease process. Ever since the report of the pot ntial reversibility of rheumatoid arthritis by Hench and isolation of this valuable steroid by K ndall, much effort has been directed toward determining the clinical value of this steroid as a specific therapeutic agent. It then becom s necessary to judge the value of this steroid by means other than subjective patient improvement or observable objective improvement. For many years, the eosinophilic sedimentation rate has been considered as one of the most valuable of laboratory adjuncts for the measurement of the index of improvement of the inflammatory activity in this disease process. With this in mind, a review of the pertinent literature concerning this subject has been attempted. A brief discussion concerning the various methods of determining sedimentation rates, the general principles involved, the factors influencing it and the various methods for correcting for variable

factors, has been presented. Particular emphasis has b en placed on a series of case reports by various authors which have been analyzed to deter mine what effect, if any, Cortisone had on the sedimentation rates in rheumatoid arthritis during different phases of therapy. Because of the great faith of most clinicians in this laboratory proced ure as a positive index of improvement of the disease entity, this writer was also interested in learning the view of basic researchers concerning the value of this test as a valid indicator. Divergent reports by skilled investigators have been offered for critical evaluation.

CONCLUSIONS

Clinical and laboratory evidence as gained by extensive study of a large series of selected patients afflict d with rheumatoid arthritis and treated by Cortisone therapy, reveals almost unanimous evidence that the st roid is of extreme value in producing clinical remissions of the disease process if correct dosage schedules are maintained. With few exceptions, almost all investigators reported significant decreases in the sedimentation rates of rheumatoid arthritics treated with Cortisone. However, certain investigators seriously qu stion the value of this laboratory procedure as a true measure or index of Cortisone effect on the inflammatory process. These workers believe that alterations produced by the direct action of the Cortisone on the gamma globulin and fibrinogen constituents of the blood with subsequent depression of these constituents and thus depression of sedimentation rat s, indicate hormonal activity only, and not the effectiveness of the steroid in reducing disease activity.

In view of these facts, reservation concerning the value of this laboratory procedure in indexing the effectiven ss of Cortisone in altering the course of rheumatoid arthritis must be considered until further biochemical physiological studies can be made. Objective and subjective clinical improvement remains as the best indicator of improvement and should be used as the criterion for guiding the therapist.

Sedimentation rates, like eosinophilic counts, can be considered as a good indicator of hormonal activity only.

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