The annual meeting of the American Rheumatism Association was held at Atlantic City, New Jersey, on June 8 and 9, 1951. The presidential address was delivered by Dr. Otto Steinbrocker of New York. Abstracts of the twenty-three papers and summaries of the discussions thereon are printed below, together with the final panel discussion on "Difficulties and Complications in the Therapeutic Use of ACTH and Adrenocortical Steroids in the Rheumatic Diseases".

**Pleuroneumonia-like Organisms and their Possible Significance in Collagenous Diseases.**


If the hypothesis that hypersensitivity phenomena are basic in the pathogenesis of collagenous diseases is accepted, the presence of an antigen, the nature of which remains to be determined, must be postulated. Pleuroneumonia-like organisms have been implicated in rheumatic diseases. Their significance as possible antigens in collagenous disease hypersensitivity states is at present under investigation.

The unique properties of human "L" organisms would satisfy the criteria of a persistent living antigen, invisible in tissues or invaded cells. These properties also preclude their direct demonstration as aetiological agents.

*In vitro* studies on 28 strains of human "L" organisms reveal marked differences in sensitivity to antibiotics, myochrysine, and nitrogen mustard.

Preliminary studies indicate that antibiotics effective *in vitro* are also effective *in vivo*. This is manifested by disappearance of demonstrable "L" organisms during administration of aureomycin, chloramphenicol, or terramycin, and by transient exacerbation of clinical symptoms of collagenous diseases. The severity of this reaction parallels the *in vitro* effectiveness of antibiotics. It can be graded by dosage or route of administration (oral or intravenous). The exacerbation is not due to drug hypersensitivity. It may represent tissue response to antigen release, induced by antibiotics. It can be modified by administration of agents interfering with hypersensitivity reactions.

**Discussion.**—Dr. Brown: During the past few years many new and hopeful remedies for arthritis have been announced, but after clinical trial and prolonged treatment, each has finally been proven either limited or useless in providing persistent, adequate control of rheumatic diseases in general. The practising physician has encountered patient disappointment and medical uncertainty on account of these failures.

We have long believed that lasting benefit would be possible only when there was a thorough understanding of the basic mechanism operating in collagen diseases in general. To date there has been no real understanding of the mechanism.

To-day we have proposed a new total concept of this mechanism, based on clinical and laboratory studies extending over the past 12 years. We suggested a new clinical approach in June, 1949, and the methods of management making use of it to-day are very encouraging, but we believe...
that we are not yet justified in drawing conclusions regarding lasting benefit. Such conclusions must depend on a sufficient number of long-term follow-up studies. This lasting benefit, or true alteration in the course of rheumatic diseases, is of the utmost importance in the evaluation of any method of management. We take this viewpoint in spite of tremendous pressure from many sides to publicize the clinical aspects in detail at this time.

We would emphasize, therefore, that our present report is directed towards the basic mechanism in these diseases. We suggest that it would be in order for the American Rheumatism Association to go on record in discouraging publicity of any new form of treatment as such in rheumatic diseases until a number of follow-up studies of at least 2 years can be assessed. We should direct more attention towards an understanding of the mechanism of collagen diseases, for we believe that to be the only way of achieving definitive lasting benefit.

**DR. MARIAN W. ROPES (Boston, Mass.):** The evidence given by Dr. Wichelhausen of the response of these organisms in vitro, and probably in vivo, to various antibiotics is interesting. In our experience we have found that there is some control in vitro, and probably in vivo, with streptomycin, which is apparently the least effective antibiotic and not very effective in our hands. Aureomycin was possibly a little more favourable. We have not tried terramycin.

I would hesitate to accept the suggestion that pleuropneumonia-like organisms are in any way related to a basic mechanism in rheumatoid arthritis chiefly because of the danger of interpreting any response to antibiotics, such as disappearance of organisms from the genito-urinary tract or change in clinical course, as any indication of aetiological relationship of the organisms to the disease.

We have been particularly interested in the relationship of pleuropneumonia-like organisms to Reiter's syndrome, and this is a field which should be studied more completely. I shall be glad to hear further reports on the use of terramycin, which is apparently the most effective in your hands against pleuropneumonia-like organisms, in Reiter's syndrome. It seems to me rather rash to interpret the response to antibiotics as any indication of the aetiological agent.

I wonder whether any studies have been made of the serological reactions to pleuropneumonia-like organisms in these patients, whether they have shown positive reactions, and whether these reactions have been changed by treatment.

**DR. WICHELHAUSEN:** In answer to Dr. Ropes' question regarding serological reactions: we have no definite data on this particular problem. I think everyone who has worked with this group of organisms knows that preparation of satisfactory antigens is still a difficult procedure. But it is possible, and work in this direction should be continued and extended. As far as the relation of change of course of collagenous diseases and aetiological agent is concerned, I agree that we should not draw hasty conclusions. In our own minds the exacerbation that follows the administration of certain antibiotics has been more important than any improvement, as far as attempts to understand the basic mechanism of these diseases are concerned. These exacerbations, possibly related to the effect of antibiotics on L organisms with subsequent antigen release into a system where antibody is readily available, have occurred with great regularity.

**Punch Biopsy of Synovial Membrane.** By Howard F. Polley and William H. Bickel, Rochester, Minn.

**Adrenal Function and Steroid Hormone Metabolism in Health and Disease.** By Konrad Dobriner, New York (by invitation).

Steroid excretion patterns in man have been studied as a means of defining the details of hormone production by the adrenals and gonads. The evidence, which correlates the metabolism of normal or abnormal adrenal hormone production in arthritis, is compared with the findings in healthy subjects and in patients with neoplastic disease. The capacity of the adrenal to respond to stimulation by ACTH, in patients with arthritis, and type and character of the response is presented. The metabolism of cortisone in an arthritic patient and the change in steroid pattern during pregnancy are correlated with the arthritic syndrome.

* This paper was published in full in the last issue of this Journal (Annals of the Rheumatic Diseases, 1951, 10, 277). Dr. Polley reported that the instrument was being manufactured without patents by V. Mueller and Co., Rochester, Minn.
Discussed.—Dr. J. J. Bunim (New York): I will give a brief clinical summary of two of the patients observed by us and included in Dr. Dobriner’s series:

1. The first patient developed rheumatoid arthritis in 1937, at the age of 43, 14 years before the steroid studies were begun. The proximal interphalangeal and metacarpophalangeal joints, wrists, and elbows were symmetrically involved, and the left ankle was severely affected. Huge subcutaneous nodules were present over the metacarpophalangeal joints of both hands and the free borders of both ulnae near the elbow. At the time of Dr. Dobriner’s studies, the sedimentation rate was 70 mm., and both the haemolytic streptococcus and sheep-cell agglutination tests were positive.

2. The second patient developed psoriasis at the age of 43 and rheumatoid arthritis 1½ years later. The onset of arthritis occurred 14 months before determination of the urinary steroids was done by Dr. Dobriner. The interphalangeal joints of the right thumb, right great toe, metatarsophalangeal joints of several toes of both feet, left wrist, and right ankle were involved. In addition, the distal interphalangeal joint of the right ring finger was swollen, red, painful, and tender. It is noteworthy that none of the proximal interphalangeal joints were affected. No subcutaneous nodules were present. Extensive psoriatic lesions were present over the back, buttocks, and posterior thighs. The erythrocyte sedimentation rate was 55 mm. per hour (Westergren). The haemolytic streptococcus and sensitized sheep-cell agglutination tests were negative.

Dr. Howard F. Polley (Rochester, Minn.): A patient from the Mayo Clinic included in Dr. Dobriner’s report was a man, aged 22, who had had rheumatoid arthritis and rheumatoid spondylitis for about 3 years. Motion in the neck, shoulders, spinal column, and knees was considerably limited. He could abduct the right arm only 65 degrees. The knees were slightly swollen. It was hard for him to put on his socks and shoes. Difficulty in combing his hair was solved by wearing a crew cut. Roentgenogram revealed bilateral sacro-iliac arthritis. The sedimentation rates were elevated. Cortisone given intramuscularly in doses of 100 mg. daily for 32 days had a marked antirheumatic effect; this began to disappear 9 days after administration of cortisone was stopped, but the patient maintained about one-half the relief for nearly 3 months.

Dr. Dobriner has given us some interesting, important and fundamental data.

Dr. Ian F. Sommerville (Edinburgh, Gt. Britain): Dr. Dobriner’s paper was of especial interest to me in the light of certain studies in steroid metabolism previously carried out by Dr. G. F. Marrian and myself in the University of Edinburgh. These studies were directed towards the problem stressed by the speaker—whether there is a relative or an absolute deficiency of adrenocortical secretion in rheumatoid arthritis. We studied the proportion of administered progesterone excreted as urinary pregnanediol as a model reaction in normal and arthritic human subjects, and we showed that an abnormally high proportion of the metabolite is excreted by the arthritic group. Progesterone was chosen because of the well-established status of its metabolite, and because there are theoretical grounds for the belief that this hormone and the adrenocortical hormones may follow at least one common metabolic pathway—the formation of pregnane derivatives and reduction of one or more ketonic groups.

This observation emphasizes the importance of extending such a study to the intermediary metabolism of cortisone itself, both in the human subject and at the cellular level; and is at least indirect evidence of an abnormal metabolism of adrenocortical hormone in rheumatoid arthritis.

Further work is in progress to establish the incidence of the abnormality of progesterone metabolism in other diseases. Preliminary observations indicate that it is not present in diseases sharing certain clinical features with the rheumatic group—for example tuberculosis, and osteoarthritis. Other diseases which respond to cortisone or ACTH have yet to be studied. As more cases are screened, we find that some arthritides fall within, or only slightly above, normal limits, and it will be interesting to correlate the degree of steroid metabolic defect with some clinical feature of the disease.

If the abnormality is indeed fundamental, then it would be expected to persist despite the administration of ACTH or cortisone. Preliminary studies with ACTH indicate that this is so.

In conclusion, I would suggest that an elucidation of the biochemical nature of this defective handling of administered steroid may lead to a significant contribution, not only to the treatment of rheumatoid arthritis, but to a better understanding of the role of the steroid hormones in pathogenesis.

Dr. J. J. R. Duthie (Edinburgh, Gt. Britain): I have been associated with the work described by Dr. Sommerville, which suggests an abnormality in cases of rheumatoid arthritis in the metabolism of steroids by the tissues. The evidence put forward by Dr. Dobriner would suggest that there is also some abnormality in the adrenal gland itself. Both conditions may be present, but the fact that the abnormal steroid metabolites disappear from the urine when ACTH and cortisone are
ANNALS OF THE RHEUMATIC DISEASES

administered is rather puzzling. That they should disappear with cortisone is understandable, but I should have expected them to increase on the administration of ACTH if the urinary metabolites are derived from an abnormal steroid produced by the adrenal. The fact that they disappear suggests the possibility that the primary defect may lie in the pituitary, which may be secreting an abnormal form of ACTH and that adrenal function reverts to normal when ACTH is given by injection. I should certainly like to hear Dr. Dobriner's views on this point.


In contrast to numerous other types of hormones, it is possible to demonstrate a localized action by adrenocortical hormones, particularly those of the C-11 oxygenated group. This spatial limitation of effect appears to be made possible by a rapid peripheral utilization of the adrenal hormones, so that, at low doses, the amount absorbed into the blood stream is insufficient to exert a systemic effect. In addition to other structures, fibro-elastic connective tissue is modified by the local action of adrenocortical steroids with all its major components involved, including cells, fibres, and ground substance. Prolonged direct application to the skin of adrenal extract causes thinning of the dermis with involution of fibroblasts, a temporary retardation in the formation of granulation tissue, and acceleration in the spreading action of hyaluronidase. These modifications are limited, for the most part, to the area of application. However, they cannot be maintained indefinitely because ultimately the skin returns to normal in spite of continuation of the treatment. Thus, a local loss in responsivity to the action of the adrenal hormones is demonstrated. When compared on the basis of their capacity to inhibit growth of hair by local action, the C-11 oxygenated steroids are more potent than the C-11 non-oxygenated steroids. Nevertheless, 11-desoxycorticosterone in large doses will inhibit the growth of hair and accelerate the spreading action of hyaluronidase. Many of the connective tissue responses to adrenocortical steroids are illustrated in striking fashion in the tissues immediately surrounding implanted pellets of pure adrenal steroids. Alterations in fibroblasts seem to be of primary significance in accounting for the other effects of adrenal hormones on connective tissue.

Discussion.—Dr. Charles Ragan (New York): I wish to compliment Dr. Baker on his paper, which is a superb piece of work.

Our main concern has been with the response of tissue to trauma as modified by the parenteral administration of cortisone, and our results corroborate those of Dr. Baker. Certainly, we can confirm everything he has said concerning the response of traumatized tissue.

However, I think that the interpretation of these results is still open to some speculation, and we, as clinicians, have found ourselves in the middle of a controversy of anatomists concerning the origin of the fibroblast, about which there are two schools of thought. The one which is most attractive, which would fit into this hypothesis, is that championed by Bloom and his school, who feel that at least one of the precursors of the fibroblasts is the macrophage. It has been shown by Dougherty and Spain that, during hyperadrenalism in animals and in humans, there is a decrease in the number of wandering cells and macrophages in an area of trauma.

Lurie and Gordon have shown that in situ the macrophage is phagocytic, Lurie in liver and Gordon in spleen. We have done this with local traumatized areas and find that in vivo the macrophage is phagocytic but does not wander into an area. The next phase in the inflammatory process has been studied by Duthie (Edinburgh), and by Bethel (Ann Arbor), who have found there is a decrease in capillary permeability after the administration of ACTH or cortisone.

The next phase in the modification of the inflammatory process has been studied by Ebert, Michaels, and Wood who have found that there is a decrease in margination of leucocytes in capillaries round an area of trauma, during hyperadrenalism. Which is the first site to be modified in this modification of the inflammatory reaction? We are not prepared to say whether one must start with the inability of the leucocytes to marginate through either the decreased capillary permeability or a decrease in the number of invading macrophages or in fibroblast proliferation.

We can confirm Dr. Baker's work, as far as the local action of cortisone is concerned, in work
done by Howes. Ear wounds were made and cortisone ointment applied to one ear and plain ointment to the other. There was a marked decrease in the granulations appearing in the cortisone-treated ear.

Concerning the escape phenomenon, whereby this is not a complete inhibition but solely a delay, we have evidence to show that this also is a local effect, since, if a wound be made in an animal made hyperadrenal with cortisone, it will heal in 14 days, but will show marked inhibition of repair after only 5 days.

I should like to ask Dr. Baker a question. Since he has demonstrated a local effect of ACE and cortisone on non-traumatized connective tissue, does he presuppose that this tissue has some turnover? In other words, do the fibroblasts disappear or is there a failure to replace them?

Dr. P. OPSAHL (New Haven, Conn.): I should like to ask Dr. Baker about the primary action on the enzyme, and whether he used adrenal extract per se or cortisone in the control.

Dr. BAKER: I am pleased to have both Dr. Ragan and Dr. Opsahl participate in this discussion, because their work has greatly stimulated us throughout our investigations.

First, a few words about the origin of fibroblasts. Dr. Ragan's comment concerning the possible conversion of macrophages into fibroblasts in the formation of granulation tissue is of extreme interest and merits investigation with respect to the action of adrenocortical hormones. However, it seems to be the opinion of most anatomists, that the majority of the fibroblasts of granulation tissue arise by proliferation of pre-existing cells of a similar or more primitive type.

With respect to the enquiry concerning the turnover of fibroblasts under these experimental circumstances, there is little that can be said. Without the employment of a technique whereby cells are tagged, I do not see how the question can be answered. Most of the results described could be explained on the basis of damage to cells which are already present due to the development of a local state of hyper-adrenocorticalism. Whether there exists a problem of turnover of cells I do not know.

As for Dr. Opsahl's question whether the primary action is on the enzyme or the cell, I should like to reiterate our contention that probably many of the changes induced in fibro-elastic connective tissue by the local action of adrenocortical steroids are due to suppression in metabolism of the fibroblast. If this is so, intra-cellular enzyme systems must be affected.

The extract used in these studies was prepared by the Upjohn Company, and is a hog adrenal extract dissolved in 25 per cent. alcohol. In all of these studies the solvent 25 per cent. alcohol was used as control.

Adrenal Cortex in Rheumatic Diseases, with Special Reference to the Effects of Cortisone and ACTH. By Leon SOKOLOFF, John T. SHARP, and Edwin H. KAUFMAN, New York (by invitation).

In a systematic study, it is demonstrated that the adrenal cortex in rheumatic diseases show no changes that distinguish it from the adrenal cortex in non-rheumatic diseases. Three types of measurements have been made:

1. weight
2. cholesterol content
3. a quantitative analysis of the zonal architecture

Control values were obtained on healthy individuals dying of trauma and of disease states of many types. Small doses (2,000 mg. or less) of ACTH or cortisone do not cause appreciable changes. Large doses of ACTH may induce marked hypertrophy that apparently regresses after cessation of therapy. Large doses of cortisone sometimes result in atrophy. The cortex may be restored to normal size when the medication is discontinued. In rheumatic diseases the adrenal responds morphologically to ACTH and cortisone in the same way as it does in non-rheumatic diseases. Permanent morphological alteration does not result from the use of these compounds.

Discussion.—Dr. M. PATTERTSON (New York): Parallel with our clinical observations of the effect of prolonged use of cortisone acetate in patients with rheumatoid arthritis, animal studies were conducted to determine whether daily injections of cortisone produced irreversible changes in the adrenal glands.

Fifty adult white rats, divided equally as to sex, were given intramuscular injections of cortisone acetate 3 mg. daily for 11 days. This dose was ten times the equivalent of a human dose of 100
mg./day and the 11-day injection period in the rat was equivalent to 1 year of life in man. Sixty-six rats provided suitable control material. The cortisone-treated rats were divided into five groups. Group I was killed at the end of the injection period to determine the probable maximal cortisone effect. The other four groups were killed at various periods after the last injection, corresponding to 4, 6, 15, and 33 months in man, and the effect of cortisone was determined by adrenal-gland weight and by histologic study of the adrenals stained by haematoxylin-eosin and Sudan IV.

Histologically the effect of cortisone upon the adrenal gland consisted of a narrowing of the cortex and a decrease in the sudanophilic material in the cytoplasm of the fasiculata and reticular zones. These were not identical in the sexes. In the male rats the effect of cortisone reached a maximum at the 6-month period and then improved, so that at 15 and at 33 months the effect was absent. In the female rats the cortisone effect present at the 1- and 4-month periods was less pronounced than in the males; at the 6-month period the females showed a slight decrease in sudanophilic material, whereas the males at this period had shown the most marked effect; at 15 and 33 months the female adrenals appeared normal.

On the basis of adrenal weight, the female rat adrenal had completely recovered after a period corresponding to 6 months in man, whereas the male adrenal was not completely normal at this period. Both sexes showed complete recovery at 15 months. The adrenal of the treated male rat always showed a greater decrease in weight as well as greater reduction in the sudanophilic substance than did the adrenal of the female rat.

These studies showed that the adrenal glands of the adult white rats injected daily with cortisone in doses ten times the equivalent of the human dose of 100 mg. a day, for a period corresponding to one year in man, completely recovered from the changes effected by the steroid. No permanent damage was found, and recovery from the cortisone effect was more rapid in the female.

Dr. E. P. Engleman (San Francisco, Calif.): I only wish to state that in patients whom we have had on cortisone therapy for as long as 14 months continuously, we have demonstrated an excellent eosinopenic response to ACTH administered intravenously, despite the simultaneous oral administration of cortisone. This was usually demonstrated in a period of 1 to 2 days.

Dr. Sokoloff: The observations of Dr. Patterson largely confirm ours. I suggest that cortisone, even in one large dose, is apparently without destructive effect upon the adrenal.

Changes in Sternal Bone Marrow and Peripheral Blood during Cortisone Therapy in Rheumatoid Disease. By Lester M. Goldman and Herman H. Tillis, Newark, N. J.

Sternal marrow and peripheral blood studies were made in 22 cases of rheumatoid disease receiving cortisone for a continuous period of 15 to 37 days. Marrow studies revealed a significant shift to maturity in granulocytes and a marked increase in the number of lymphocytes at the end of the period of observation. The changes seen in various leucocyte levels in the peripheral blood during the period of observation were discussed. It was suggested that an anti-inflammatory action of cortisone may explain an initial lymphopenia and subsequent lymphocytosis.

Discussion.—Dr. J. J. Bunim (New York): The importance of the observation reported by Dr. Tillis and Dr. Goldman depends on the significance of the changes observed. It is also important to bear in mind that the difference in the number of cells is relative not absolute. Was the shift observed after cortisone administration associated with an increase in the total cellularity of the bone marrow, and if so, how did it affect the myeloid-erythroid ratio and the lymphocyte-erythroid ratio? If, for example, there were an increase in cellularity, and if, furthermore, the erythroid elements remained constant, then an increase in the lymphocytes and/or the mature granulocytes would account for a resulting fall in the relative percentage of immature granulocytes. In such circumstances, it would not be valid to conclude that cortisone inhibited the normal reaction to inflammation. That cortisone administration is followed by a recession of the inflammatory reaction in tissues such as the synovial, the subcutaneous nodules of rheumatic fever, and the corium in certain rheumatic diseases, has been demonstrated repeatedly. It has also been shown by Wood that at the site of bacterially-induced inflammation, cortisone depresses the process of cellular exudation. The lesions consequently contain relatively acellular oedema-fluid in which many more bacteria are present than in the lesions from control animals. Exactly such histopathological circumstances were observed in one of our patients who died of an overwhelming pneumococcal pneumonia while under ACTH therapy.
To attribute to cortisone the capacity to inhibit in the bone marrow a natural granulocytic response to inflammation, may lead one erroneously to shift the emphasis from the local inflammatory lesion to a haematopoietic structure, as the important site of cortisone action. The results reported by Dr. Tillis and Dr. Goldman are at variance with those published last year by Rosenthal, Yager, and Litwins of New York. The differential counts in the bone marrow of a series of patients with rheumatoid arthritis treated with cortisone by these workers showed no significant change. For example, before and after cortisone, the myelocyte count was 22 and 24 per cent., the non-segmented neutrophil count was 30 per cent., the segmented neutrophils were 14 and 13 per cent., and the eosinophil count was 3 per cent. More recently, Sussman and Antopol conducted similar studies in cortisone-treated mice and again found no "inhibitory effect of cortisone on cell proliferation in the bone marrow".

We should like to ask Dr. Tillis whether the fall in the immature granulocytes may not have been secondary to a relative increase in the lymphocytes or mature granulocytes. Is it not possible that the lymphocytosis in the bone marrow was secondary to the lymphopenia in the peripheral blood? Would not the hypothetical anti-inflammatory effect of cortisone imply an inability of the bone marrow to respond adequately to an intercurrent infection?

Dr. C. L. Steinberg (Rochester, N.Y.): What interested me was not so much the lymphocyte response that Dr. Tillis emphasized, but the change in the plasma cells. If you recall, he reported that the plasmacytes increased to an average of 0.6 from 0.3 per cent.; and if one recalls that the plasmacytes are markedly increased in the bone marrow in the disease multiple myeloma, and that in the same disease the gamma globulin is markedly elevated, and if one keeps in mind that gamma globulin is intimately associated with the immune response, then certain conclusions may be drawn.

Gamma globulin is increased in disseminated lupus erythematosus, which is the opposite of what one would expect. The total globulin is usually elevated, and when the response to either ACTH or cortisone is obtained, the total globulin drops. Other observers have seen the same thing to occur in rheumatoid arthritis.

It seems to me that one of the reasons for the discrepancy given this morning is the fact that 500 cells are insufficient to count, since at least 5,000 cells are required in order to be reasonably accurate as to the haematological picture that is present in the bone marrow.

Lastly, I wish to bring up a controversial point. Are the lymphocytes produced in the bone marrow? The bone marrow has been diluted with peripheral blood by this method, and we are not getting a true picture of what is occurring in the bone marrow.

Dr. Abraham S. Gordon (Brooklyn, N.Y.): I want to ask Dr. Tillis what method he used in the study of the contents of the bone marrow. I think the entire picture of the changes noted depends upon the method used in the study of the cellular content of bone marrow, but that is not described. Can he give us any details on this matter? How did he dispose of the intercellular substance, or the walls of the sinuses of the marrow, and how did he dispose of the fat in the marrow?

I call attention to this because about fourteen years ago I described a special method of studying cellular contents of marrow and went into great detail to eliminate all the extraneous material so as to be able to show exactly the differential elements in the different types of the cells in the marrow. I therefore think the method used is extremely important.

Often unidentified cells or very early primordial cells are mistaken for lymphocytes. The results may vary, depending upon the technique. I have seen some of these data on the screen and they are completely at variance with some of my findings when studying the marrow.

Dr. Tillis: As regards the erythroid elements, we felt we could arrive at no conclusions. It must be realized how this study was started. It was done in a routine examination early in 1950, when we were trying to evaluate patients who had taken cortisone; at that time we did not know what the effect of cortisone on the bone marrow was going to be, any more than we knew what its effect was going to be on the spinal fluid which we studied. We felt that because of the transfusions and the haematotics we could arrive at no conclusions regarding erythroid elements, and therefore made no effort to do so.

Regarding eosinophil studies on mice, the dosage that was used over a period of 17 days was so tremendous that I feel that no other observer can compare them with the human from that standpoint.

Regarding the technique of bone marrow aspirations, Dr. Goldman performed these in the manner that is usual in our hospital.

Our findings showed an increase of the lymphocytes in the bone marrow after cortisone therapy.
Aortitis and Aortic Endocarditis, an Unrecognized Manifestation of Rheumatoid Arthritis.

By Walter Bauer, William S. Clark, and J. Peter Kulka, Boston, Mass.

The onset of pericarditis and subsequently aortic regurgitation during an exacerbation of rheumatoid arthritis, first observed some years ago, called our attention to the possibility that carditis may be a manifestation of rheumatoid arthritis. Additional evidence favouring this postulate had been noted previously; namely, that our rheumatoid arthritic patients with valvular heart disease had a higher incidence of aortic regurgitation than did a comparable group of patients with rheumatic heart disease.

Since then we have accumulated sufficient data to permit us to conclude that aortitis and aortic endocarditis do occur as a manifestation of rheumatoid arthritis. The clinical and pathological features of this type of heart disease are sufficiently distinctive to exclude syphilis and rheumatic fever as aetiological agents.

Discussion. — Dr. Theodore B. Bayles (Boston, Mass.): We have all been interested in this report on the presence of heart disease associated with rheumatoid arthritis. The figures given concur closely with what we reported 8 years ago, and it is obvious that the inflammatory reaction in connective tissue in rheumatoid arthritis can occur in and about the heart as it does in other parts of the body. We did not observe this significant aortic lesion reported this morning.

Dr. Edward F. Rosenberg (Chicago, Ill.): Among the cases studied some years ago by Dr. Baggenstoss, Dr. Hench, and me, were two instances in which the heart showed nodular lesions similar to those described this morning by Dr. Bauer. We considered these distinctive in appearance from other inflammatory lesions observed in the hearts of this group and we compared them to subcutaneous nodules of rheumatoid arthritis. We considered these a special cardiac lesion of rheumatoid arthritis. I agree with Dr. Bauer that serious heart disease is commonly present in rheumatoid arthritis patients, and that is for some reason rarely detected by our present clinical examinations.

The question whether rheumatic fever is related to rheumatoid arthritis, is still an open one in my mind. In a majority of the cases, pathological lesions encountered in the hearts of persons dying with rheumatoid arthritis cannot be distinguished by capable pathologists from the classic lesions of rheumatic fever.

Dr. Granville A. Bennett (Chicago, Ill.): For the purpose of this meeting, I should like to record one other instance of an aortic lesion in association with rheumatoid arthritis. This was in a young boy who developed progressive rheumatoid arthritis at something less than 3 years of age. The arthritis progressed rapidly and extensively, so that at the time of his death, at the age of 8, he was crippled and deformed, and had also contracted a panophthalmitis which resulted in blindness in one eye.

At autopsy it was found that he had a marked aortitis with early aneurysm formation. On histologic examination the aortic valve showed thickened cusps, and the proximal portion of the aorta for a distance of about 3 cm. showed changes practically identical with those described by Dr. Bauer. This lesion, as he pointed out, is exceedingly difficult, if not impossible, to distinguish morphologically from an active syphilitic aortitis. However, in this case, as in Dr. Bauer’s cases, there was no evidence of syphilis. Careful serological studies gave negative results and there was no historical evidence of syphilis.

I think that in both these cases we are dealing with instances of rheumatoid arthritis in which the connective tissue structures of the aorta have been selectively involved. There were no lesions in our patient to suggest rheumatic fever.

In another case there were signs of polyserositis and periartthritis in association with rheumatoid arthritis, but in this instance there was a marked overlap between the various types of connective tissue disease and rheumatoid arthritis.

Dr. Wallace Graham (Toronto, Canada): I should like to ask Dr. Bauer whether he has observed these lesions in any patient suffering from pure rheumatoid arthritis. Unless I am mistaken, all the cases presented have had spondylitis. To those of us who still feel that there are good reasons for separating rheumatoid arthritis from ankylosing spondylitis, these aortic lesions occurring only with spondylitis would appear to furnish additional evidence of a clear-cut difference between the two conditions.

Dr. Charles W. Wainwright (Baltimore, Md): Were there lesions in other tissues which might simulate lupus erythematosus?
A MEMBER: Has Dr. Bauer employed histamines?

DR. J. J. R. DUTHIE (Edinburgh, Scotland): It seems to me significant that in all the cases described by Dr. Bauer the spine was involved. In Britain we still tend to the opinion that rheumatoid arthritis and ankylosing spondylitis are different diseases, although we are well aware that similar changes in the peripheral joints may occur in both.

DR. CHARLES RAGAN (New York): I should like to know whether these patients with spondylitis had typical rheumatoid nodules.

A MEMBER: I should like to ask Dr. Bauer whether these were uniform findings in all the various parts of the heart and whether they were examined in different sections.

I should also like to ask him if any Aschoff bodies were present in any of the hearts that he examined, and to the question that has just been asked, whether the same lesions were not found in other parts of the vascular system or in other parts of the body.

DR. BAUER: I called attention to the fact that although all patients had spondylitis, approximately 75 per cent. of them also had peripheral joint disease. To date, we have not seen this type of valvular heart disease in patients with only peripheral joint involvement. In two cases the peripheral joint disease was so marked that the minimal spondylitis might have been overlooked. In some of these patients the disease began in the peripheral joints, and evidence of spondylitis was not seen until some years later. Cases of this type indicate the need for determining the incidence of spondylitis in rheumatoid arthritis of the peripheral type. This can only be established by obtaining routine X rays of the spine in a large number of such cases.

Our group has always considered spondylitis as a form of rheumatoid arthritis and not as a distinct disease entity. We admit that the absence of nodules and the predominance of males in patients with spondylitis favour the latter point of view. However, much about rheumatoid arthritis remains unknown, and until these gaps in our knowledge are filled, we cannot explain exceptions or establish additional disease entities.

Regarding lupus erythematosus, the answer is No.

We have treated two such cases with ACTH without favourable effect on the heart disease.

One of the patients with pericardial nodules had approximately one hundred subcutaneous nodules, but no nodules were found in the myocardium of the cases here reported, though they have been observed by Rosenberg and others.

Chemical and Histological Studies of the Fibrinoid Material of the Subcutaneous Rheumatoid Nodule. By THOMAS KANTOR, LEON SOKOLOFF, ALFRED SMITH, and MORRIS ZIFF, New York (introduced by Dr. Currier McEwen).

The concept of collagen disease requires a detailed consideration of the composition of fibrinoid since the fibrinoid change is the anatomical common denominator of conditions grouped under this concept. Methods have been devised in this laboratory for the separation of fibrinoid from the remaining connective tissue structures of the subcutaneous rheumatoid nodule. Using 1 to 2 mm. slices or minces of this tissue, it has been found that the fibrinoid regularly present is readily separated by treatment with 0·1 N NaOH or crystalline trypsin solutions. Serial sections have been made of the material remaining after 24-hour extraction. With conventional staining techniques known to characterize fibrinoid, it is estimated that at least 80 per cent. of the fibrinoid material has been removed by these methods. In contrast, borate buffer solutions at pH 7·8, streptokinase-activated plasmin, and testicular hyaluronidase solutions remove only very small amounts of fibrinoid. The separated extracts have been analysed for hydroxyproline by the radio-iodine isotope derivative method of Keston and others, which is sensitive to 0·1 gamma hydroxyproline. In analyses of two nodules by this technique, only trace amounts of hydroxyproline were found in the extracted fibrinoid. This suggests that the fibrinoid of the subcutaneous rheumatoid nodule is non-collagenous in origin. In support of this point of view, it has been observed that fibrinoid material in sections of the subcutaneous rheumatoid nodule is not digested by a very active clostridial collagenase.

Discussion.—DR. J. P. KULKA (Boston, Mass.): I want to compliment Dr. Kantor and his associates for showing so elegantly that fibrinoid is not of collagenous origin.

One point that Dr. Kantor made indirectly I should like to emphasize, namely, the distinction
between fibrinoid, a morphologically distinct substance, and fibrinoid degeneration, a term which, as originally used, combines

(i) the presence of fibrinoid,
(ii) the connective tissue changes which are frequently associated with fibrinoid,
(iii) the hypothesis that fibrinoid is derived from a chemical change in the intercellular substances.

This combination in a single term of three different meanings has, I think, caused considerable confusion in the literature.

Dr. Kantor talked about fibrinoid, the morphologically distinct substance. He has demonstrated a type of approach by which we may be able to determine the chemical nature of this substance. The next step will be to determine the nature of the relationship between fibrinoid and the degenerative changes in the connective tissue, which are the most obviously damaging features of the rheumatic lesions.

Dr. Granville A. Bennett (Chicago, Ill.): Some years ago, when being pushed to state what fibrinoid is, I could think of nothing better to say than that it represents something added to connective tissue, perhaps only plasma soaking of connective tissue. I feel that the present study lends support to the concept some of us have had that fibrinoid is not strictly a change in the composition of collagen.

I think that fibrinoid change—and I prefer to speak of it as fibrinoid change rather than fibrinoid degeneration since we do not know just what the alteration is—is seen in various stages of development. The lesions that were demonstrated so beautifully this morning, are possibly late lesions. If we were to look at some of the earlier lesions we might find material that stains histochemically in the characteristic fashion of fibrinoid, but we might see connective tissue fibrils extending completely across the lesion at the same time.

In what we consider to be older lesions, complete breakdown of all the connective tissue substances occurs in the centre of the nodules. In fact, some lesions become cystic and may contain only yellowish, amorphous, glandular or curdlike material in their centres.

Thus the degree of change or the amount of disintegration of connective tissue depends, I believe, upon the duration of the lesion. The older nodules show the most complete breakdown.

I hope you will comment on your findings in light of the stages of development of the nodules.

Dr. Currier McEwen (New York): I can add only the comment that most people have been somewhat dissatisfied with the term "collagen diseases" and that this is perhaps one more reason to be dissatisfied with it.

Dr. Hugo A. Freund (Detroit, Mich.): I am glad that the distinction was made between the formation of fibrinoid and fibrinoid degeneration. Fibrinoid is formed in so many different conditions. We have been particularly interested in fibrinoid in our pathological laboratories, because we know that fibrinoid is found in many allergic manifestations, in the Aschoff body, in lymphocytic accumulations, and, as discussed to-day, in subcutaneous nodules. Altshuler and Angevine (1949) suggested the possibility of fibrinoid formation coming originally from the acid mucopolysaccharides. In that connection, we have studied, and recently reported, that in rheumatoid arthritis an excessive formation of mucoproteins and mucopolysaccharides occurs. Methods of measuring the mucoprotein have been devised, though we are not yet certain about their accuracy.

I should like to offer the suggestion that mucoproteins and mucopolysaccharides are the precursors of fibrinoid which in time undergoes degeneration, and that the entire process is initiated by a hormonal defect or by a failure of a specific enzyme formation.

Dr. Kantor: First of all, Dr. Freund mentioned the role of the intercellular ground substance in the production of fibrinoid and referred to Altshuler and Angevine (1949). We certainly confirm the findings of Altshuler and Angevine; all sources of fibrinoid that we have examined are positive with the periodic acid-leuco fuchsin stain after appropriate controls to eliminate glycogen and lipids. Most investigators believe this indicates the presence of an acid mucopolysaccharide. We are now trying to design a way of treating our nodule minces in order to determine the acid mucopolysaccharide content of the fibrinoid. This will probably be a difficult job since, by our methods, we almost certainly remove the ordinary tissue mucopolysaccharides as well as the fibrinoid. In any case, this will only resolve the question of concentration; it neglects what may be more important—namely, the physical and chemical state of these substances.

Dr. Bennett points out, quite correctly, that our tissues represent late lesions. They are all

from nodules that have been present from 1 to 3 years. However, we were quite definite in picking solid, and therefore, presumably younger, portions of the nodules for analysis. In fact, only one of the nodules had cystic change in one portion.

Dr. Bennett’s point about the earlier lesions looking as though they were “painted” with fibrinoid material is a good one. We think that is probably what the process represents. Once one takes the fibrinoid material out, normal collagen is apparently left underneath. It is as though fibrinoid material were absorbed on to the collagen fibres.

We did have one early lesion which had been present for a week or 10 days, but to our dismay, we lost it because of technical difficulties.

Dr. McEwen pointed out that the concept of collagen disease is perhaps seriously affected by this work. Klemperer (1950, 1951) has pointed out the inherent dangers in this concept. His concept of collagen disease has little to do with the protein collagen itself. He originally meant, in the older pathological sense, to include an equal consideration of all of the intercellular elements of the connective tissue. Thus, he includes in this concept the ground substance elements and elastin as well as the collagen fibre.


Injection of 25 to 50 mg. cortisone directly into the synovial cavity of one inflamed knee joint in each of eleven patients with rheumatoid arthritis caused no local beneficial effects as measured by symptoms and physical signs, by lowering the cell count of the synovial fluid, or particularly by a significant reduction (i.e. more than 0.4°C) in intra-articular temperature. In contrast, the administration of 25 mg. Compound F (Kendall) into a single diseased joint in each of nine patients with rheumatoid arthritis resulted in marked local improvement in symptoms and signs, a fall in the cell count of the synovial fluid, and a significant fall (0.6°C to 1.9°C) in intra-articular temperature within 24 hrs. Contralateral diseased joints used as controls showed no significant change, nor were there other signs of systemic effect.

In two patients a measurable benefit was noted with doses of 10 to 15 mg. Compound F, but most required 25 mg. The joint temperature returned to pretreatment level within 48 hrs in most instances. Some clinical improvement persisted as long as 10 days after a single injection of 25 mg. Compound F into the joint. It would appear that the demonstration of a direct action and beneficial effect of Compound F, in apparent contradiction to Compound E, upon the tissues of the rheumatoid arthritic joint, further emphasizes the physiological importance of Compound F.

Discussion.—Dr. Carl Stevenson (New York): We have had experience with the intra-articular injection of Compound F acetate in fourteen patients with rheumatoid arthritis; one had injections into the hip joint, and the others into the knee joints. The initial dose was always 25 mg., with subsequent doses of 25 or 50 mg. Injections were made at intervals of from 3 to 42 days. The short intervals occurred during the early part of this study when an attempt was made to suppress all signs of inflammation in the treated joint. In this group of patients, twelve of the fourteen reported more than 50 per cent. relief from pain and stiffness; six patients reported complete relief of symptoms when injections were made weekly.

The degree of symptomatic improvement did not always parallel the objective changes. In most instances the patient reported relief from pain and stiffness before there was a significant change in the physical signs. There was, however, a moderate to complete improvement in the injected joints of eleven of the fourteen patients. During the interval between injections, objective worsening appeared 2 to 14 days before symptomatic worsening.

These preliminary studies suggest the following generalizations:

(1) Compound F can be given safely into the joint cavity.
(2) It has a local suppressive effect on joint inflammation as measured clinically in most patients.
(3) Evidence that the effect is local is shown by the complete absence of changes in other joints.
(4) 50 mg. Compound F acetate usually produced a greater improvement than doses of 25 mg.


7
ANNALS OF THE RHEUMATIC DISEASES

(4) Aspiration of all conveniently available fluid from the joint prior to injection of Compound F seemed to enhance beneficial effect.

(5) The average duration of improvement was between 10 and 20 days after injection; two patients showed improvement for 28 and 42 days respectively.

(6) The cell count of joint fluid showed a decrease in total cells with a return of lymphocytes in all patients.

DR. MARIAN W. ROGERS (Boston, Mass.): Dr. Hollander’s report of the temperature changes in cortisone and Compound F are clear-cut. Has he any explanation of their meaning as regards the physiology of the joint.

We have not tried Compound F, but have given cortisone by intra-articular injection to three patients. All had some subjective and objective improvement, but we found that the cell count in the synovial fluid was usually the same or slightly elevated. The polymorphonuclears fell in one case, and viscosity rose in all cases, to the same degree as one would expect from intramuscular or oral cortisone.

There were two unusual findings: in one patient with bilateral knee effusions, radio-active sodium entered more rapidly into the treated joint than into the opposite joint, which perhaps indicates increased inflammation in the joint into which cortisone was injected. In another patient the electrophoretic pattern of fluid showed a remarkable change: the gamma globulin fraction rose from 20 to 25 per cent, and the albumin dropped from 39 to 34 per cent.

DR. DAVID H. KLING (Los Angeles, Calif.): I have given intra-articular injections of cortisone in a large number of cases; the doses varied from 50 to 100 mg. repeated after 48 to 72 hours. Various degrees of clinical improvement were found in the majority. Re-aspiration showed a diminution of inflammation: increase in viscosity, and decrease of total cell counts and polymorncellar leucocytes. However, the effects were of no longer duration than after intramuscular injections, which was disappointing as we had hoped that a depot of cortisone in the joint cavity would be only slowly absorbed and would thus have a prolonged effect. Re-aspiration 48 hours after injection showed that the effusion contained a sediment of granular and crystalline material derived from the injected cortisone. Samples of this sediment were submitted for analysis to the Merck Laboratory, and Dr. Gibson informed me that they were unable to identify cortisone in the material.

Disintegration of cortisone by the metabolic activity of inflamed synovial tissues may explain the failure to prolong its therapeutic effect by intra-articular injections.

However, I cannot subscribe to the idea that cortisone has only a systemic effect while Compound F exerts a powerful local action. This is contradicted not only by our own experience of the immediate beneficial effect of intra-articular injections but also by the pronounced effect of local application of cortisone in some eye conditions.

Intra-articular temperature measurements are valuable but are not the only reliable indicators of inflammatory activity in the joint cavity. Clinical aspects, such as swelling, stiffness, tenderness, local skin temperature, and analysis of joint effusions, are of equal or greater importance.

DR. J. J. BUNIM (New York): Injection of 50 mg. cortisone acetate into the knee joints of twelve patients with rheumatoid arthritis resulted in eight in marked to moderate improvement locally. The pain, swelling, stiffness, and effusion diminished or disappeared. In the remaining four patients, there was no improvement. When cortisone was introduced into the knee several weeks after the patient had been receiving cortisone by mouth or intra-muscularly, local improvement in the articular symptoms was definitely augmented. Therefore, if it be reasoned (but this is all theoretical), that cortisone given systematically reaches the articular tissues as Compound F, it would then appear that, in the absence of evidence that synovial tissue in rheumatoid arthritis has the ability to reduce Compound E to Compound F, larger amounts of “E” are more effective than smaller amounts of “F”. In other words, if there is a difference in the action of these compounds, it would seem to be a quantitative one.

It has recently been demonstrated by Kornofsky of the Sloan-Kettering Institute that the differences between the biological effects of cortisone and Compound F vary in different experimental animals. Whereas, in the chick embryo, Compound F was found to be 30 times, and in the newly-hatched chick about 100 times, more active than cortisone, in new-born mice cortisone and Compound F were found to have the same degree of biological activity. Dr. Heard arrived at a similar conclusion when assaying these two hormones by several different techniques in mammalian systems.

In a patient with rheumatoid arthritis 50 mg. Compound E acetate was injected into one knee and 50 mg. Compound F acetate into the other. The synovial fluid from each joint was analysed before and after each injection and in addition to total and differential leucocytes counts, the
activity of an amino-peptidase enzyme in the synovial fluid which splits glycyl-glycyl-glycine was also determined (see Table). I should like to add here that, although studies on the enzyme activities of synovial fluid in our laboratory have not yet been completed, our results hitherto indicate that the concentration of amino-peptidase in the synovial fluid is probably related to the type and density of cellular infiltration in the synovial tissue. In general, synovial fluid from rheumatoid and tuberculous joints contain significantly greater concentrations of peptidases than fluid from patients with rheumatic fever, or gonococcic, traumatic, or osteo-arthritis.

The peptidase activity of serum was 5·9 before, and 7·8 after, cortisone administration. It is our impression that cortisone injected intra-articularly is of definite value in properly selected cases, but further experience may prove that compound F is more effective.

<table>
<thead>
<tr>
<th>Knee</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone</td>
<td>Cortisone Acetate (50 mg.)</td>
<td>Compound F Acetate (50 mg.)</td>
</tr>
<tr>
<td>Time of Assessment</td>
<td>Before Therapy</td>
<td>After 14 days on Oral Cortisone</td>
</tr>
<tr>
<td>Subjective</td>
<td>—</td>
<td>Slight</td>
</tr>
<tr>
<td>Objective</td>
<td>—</td>
<td>Slight</td>
</tr>
<tr>
<td>Total white blood cells</td>
<td>16,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Per cent. polymorphs</td>
<td>79</td>
<td>98</td>
</tr>
<tr>
<td>Per cent. lymphocytes</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Peptidase activity*</td>
<td>19.6</td>
<td>16.1</td>
</tr>
</tbody>
</table>

*Expressed in per cent. glycyl-glycyl-glycine hydrolyzed per hour.

**Dr. B. F. Masell (Boston, Mass.):** Was the vehicle used the same?

**Dr. Edward W. Boland (Los Angeles, Calif.):** For the past 2 months we have been investigating the effects of Compound F acetate given systemically by both the oral and intramuscular routes in patients with chronic rheumatoid arthritis. Our experience has been very limited, but so far Compound F acetate has not been found to be superior to cortisone in its antirheumatic activity. Our preliminary observations indicate that the amount of Compound F acetate needed for equivalent response may be greater, milligram for milligram. From the standpoint of adverse reactions, however, less psychic stimulation has been experienced than with cortisone. We have had no experience with Compound F used intra-articularly.

**Dr. William D. Robinson (Ann Arbor, Mich.):** Are the comparative studies for Compound E (cortisone) based on the changes occurring in 24 hrs after a single injection, or on the basis of repeated daily injections?

**Dr. William S. Clark (Boston, Mass.):** It is our impression, on the basis of limited experience, that Compound F, milligram for milligram, is equally as effective as Compound E, and that any differences in antirheumatic effects may be due to the factor of absorption. Have studies been made to determine relative rates of absorption from the joint of these two compounds. We stopped our study with intra-articular cortisone, because, on the basis of eosinophil counts, we did not feel we were keeping the hormone in the joint long enough to get a local effect. If Compound F is absorbed more slowly, its local effects may be due rather to having a higher concentration in the joint for a longer period, than to any qualitative differences between the two hormones.
Dr. Hollander: We feel that the joint temperature is only a measurement of the amount of inflammation present in that joint.

With regard to Dr. Kling's question, I am amazed at the amounts of cortisone he was able to inject without reaction. We have always noted reaction to doses of Compound E greater than 25 mg., and we have not yet tried doses of Compound F larger than 37.5 mg.

Referring to Dr. Bunim's case, which showed equal effects, with E and F, we have tried two such experiments with E in one joint and F in another, in cases already on cortisone. I think that the results of such an experiment are open to question. When you inject 50 mg. F into one knee and 50 mg. E into the other, there is no question that the addition to the systemic cortisone already used will have increased systemic effects which will certainly affect both knees.

In answer to Dr. Massell's question about the vehicles used, the two preparations used were E and F acetate, and the particle size was identical. We tried experiments using E alcohol, which is ten times more soluble than E acetate, and we tried cortisone tricarballylate solution locally, but neither was comparable to F acetate in local anti-inflammatory effect.

In response to Dr. Boland's remark about systemic Compound F being inferior to E, we, too, have observed less striking effects from F in the few cases we have treated systemically. We feel it may be necessary to give F frequently, in smaller doses, rather than in the single large doses of cortisone which we have been accustomed to use.

Concerning Dr. Robinson's comparison studies: in our experiments we have tried to cover the effects of both single and multiple injections. Most of our clinical effects were measured on the basis of one injection, observed until the patient experienced a partial relapse, followed by another one, and so on—not pyramiding the injections, but waiting until the first effect was over, as we wanted to see how long the benefit would last.

In answer to Dr. Clark: as far as I know the rate of absorption from the tissues of Compound F as compared with E, has not yet been worked out, and we have not yet determined the absorption rates from the joints.

I want to close by saying that we do not claim that Compound F used locally is a treatment for arthritis, nor that it has anything to do with the cause of arthritis, but the ameliorating effect is an interesting phenomenon and worthy of further study.

Significant Remissions in Rheumatic Diseases with High-Dosage Cortisone Therapy. By Theodore B. Bayles, Francis L. Colpoys, Paul Fremont-Smith, Bruce C. Ferguson, and Emil Paige, Boston, Mass.

After standard dosage ACTH and cortisone therapy in rheumatic diseases, 90 per cent. of 135 patients relapsed within 10 days after treatment. Nine patients on ACTH therapy experienced prolonged remissions. Accordingly, we treated twelve patients with high-dosage cortisone: seven cases of rheumatoid arthritis, one of rheumatoid spondylitis, one of juvenile rheumatoid arthritis, two of disseminated lupus erythematosus, and one of smouldering rheumatic fever with carditis. Previously the standard dosage of ACTH or cortisone had failed to produce lasting improvement in four.

500 mg. cortisone were administered intramuscularly daily for 14 to 28 days, to eleven adults; the juvenile rheumatoid arthritis patient received 300 mg. daily. Transient psychotic episodes in two patients and marked fluid retention in a third were the only serious temporary effects noted.

The first five patients treated were followed up for 74 to 88 days after therapy and all are in good clinical remission with no evidence of persisting hormonal effect.

Four patients followed for 13 to 32 days are in good clinical remission. Three patients have just concluded therapy.

The prolonged remissions are highly significant in view of previous experience. High-dosage therapy can be administered with safety and deserves further investigation.


Since our first report on prolonged cortisone treatment for rheumatoid arthritis was made in June, 1950, experience has been gained in many more patients and for longer treatment periods; in some patients there was uninterrupted treatment for 12 months or
longer. Also, experience has now been gained with the clinical course after prolonged hormone treatment has been discontinued.

Early and severe relapse of the disease after cessation of cortisone was the rule even after prolonged treatment and in patients with disease in short duration, no matter how the hormone was given. Entirely separate from relapse of the arthritis is the problem, in some patients, of severe and prolonged "post-cortisone withdrawal syndrome". Therefore, the importance that the hormone be not considered routine treatment in patients with rheumatoid arthritis is emphasized and the necessity is stressed that the following two questions (not one), be considered before cortisone treatment is decided upon:

1. What will happen when cortisone is administered?
2. What will happen when the hormone is discontinued?

Clinical Effects of Cortisone administered orally to 100 Patients with Rheumatoid Arthritis.


The effects of tablets of cortisone administered orally have been studied in about 100 cases of rheumatoid arthritis. In all patients the antirheumatic effect was comparable to that resulting from the intramuscular administration of cortisone.

In most instances the required dose of cortisone was approximately the same for the oral as for the intramuscular preparation. Some cases required slightly more of the oral than of the intramuscular material. Occasionally oral cortisone seemed more effective.

The main difference between the effect of oral and intramuscular cortisone was the greater speed of onset and the more rapid wearing off of the antirheumatic effect in the case of oral cortisone. The daily dose of oral cortisone should be divided and spaced more or less equally throughout the 24-hr period.

Side-effects resulting from oral administration were similar qualitatively to those seen in cases treated by the intramuscular injection. The incidence of side-effects depended largely upon the factors of dosage, duration of treatment, and susceptibility of the patient. In a very few cases some gastro-intestinal irritation followed oral administration.

In many cases it was possible to maintain a good antirheumatic effect by the use of relatively small doses of oral cortisone which did not lead to the development of significant side-effects during the several months of administration.

Discussion.—Dr. E. P. Engleman (San Francisco, Calif.): In order to evaluate their adrenocortical function, fourteen patients given cortisone for long terms were given ACTH intravenously for periods of 3 to 12 hours. In each patient so tested, adrenocortical function was manifested by excellent eosinopenic response to ACTH, despite the continued ingestion of cortisone. The data are presented in the Table.

It appears that irreversible adrenal atrophy is not a likely result of long-term treatment with cortisone when the prescribed maintenance doses are used. It must be noted, however, that more than one intravenous injection of ACTH was often required in order to demonstrate adrenal responsiveness. The slower than normal response to intravenous ACTH is compatible with the observation that there is a depression of adrenal cortex function during therapy with cortisone even when small doses of cortisone are used.

Dr. E. F. Hartung (New York): I agree with almost every detail of what was said by Dr. Freyberg and Dr. Slocumb. My own experience extends over 17 months, in about 100 cases. In only 35 per cent. of the cases, in my experience, can we maintain a patient in reasonable comfort with a safe dose. In all the others, we are squeezed between two millstones; that is, if we give a large enough dose to keep them in reasonable comfort we produce untoward effects. Thus my results are somewhat less optimistic than those of Dr. Freyberg.

My feeling is that the safe maintenance dose is much less than 75 mg. a day. If one goes over 50 mg., in four or five divided doses, one sooner or later gets into serious difficulties.

Also, about 6 per cent. of our cases were what might be called cortisone failures, in that the effect was so ephemeral, lasting only a week or two, that it was hardly worth while to the patient, and in spite of large doses, the patient continued to be severely ill.
ANNALS OF THE RHEUMATIC DISEASES

One last point. I still hold that gold salts occasionally produce an arrest in rheumatoid arthritis, and, in my experience, cortisone therapy militates against the beneficial effects of gold salts, even when cortisone has been temporarily discontinued, and for a long time thereafter.

### TABLE

**EOSINOPHIL RESPONSE TO DAILY SLOW INTRAVENOUS ACTH, 25 MG., IN RHEUMATOID ARTHRITIS PATIENTS RECEIVING CONTINUOUS CORTISONE THERAPY FOR 9 TO 14 MONTHS**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Daily Dose Cortisone (mg.)</th>
<th>Months of Cortisone Therapy</th>
<th>Duration of Daily I.V. (hours)</th>
<th>Day of Eosinopenic Effect</th>
<th>Eosinophil Counts on Day of Significant Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.B.</td>
<td>50</td>
<td>11</td>
<td>12</td>
<td>2nd</td>
<td>374</td>
</tr>
<tr>
<td>F.H.</td>
<td>37½</td>
<td>14</td>
<td>3</td>
<td>2nd</td>
<td>330</td>
</tr>
<tr>
<td>A.L.</td>
<td>75</td>
<td>12</td>
<td>2nd</td>
<td>220</td>
<td>70</td>
</tr>
<tr>
<td>L.L.</td>
<td>87½</td>
<td>10</td>
<td>3</td>
<td>2nd</td>
<td>220</td>
</tr>
<tr>
<td>W.L.</td>
<td>100</td>
<td>14</td>
<td>12*</td>
<td>2nd</td>
<td>431</td>
</tr>
<tr>
<td>E.M.</td>
<td>75</td>
<td>11</td>
<td>12*</td>
<td>2nd</td>
<td>572</td>
</tr>
<tr>
<td>J.R.†</td>
<td>37½</td>
<td>9</td>
<td>12</td>
<td>2nd</td>
<td>110</td>
</tr>
</tbody>
</table>

* Duration of I.V. ACTH on previous day(s) had been 3 hours.
† Diagnosis: Chronic bronchial asthma.

DR. EDWARD W. BOLAND (Los Angeles, Calif.): Dr. Headley and I recently completed an analysis of our results with prolonged uninterrupted cortisone therapy in 76 patients with rheumatoid arthritis. Sixty were given cortisone continuously for periods ranging from 6 to 15 months, and 27 were treated uninterruptedly for more than one year. In the remaining sixteen patients, treatment was stopped within 6 months because of inadequate results or the development of undue hormonal complications. Our overall statistics are thus very similar to those presented to-day by Dr. Freyberg and Dr. Slocumb.

Of the entire group of 76 patients it was possible to maintain satisfactory degrees of improvement for long periods in 48, approximately two-thirds of the total.

The likelihood of promoting and sustaining satisfactory improvement depended on the initial severity of the rheumatoid arthritis more than on any other single factor. This, we think, is important, and we believe that the correlation of disease severity to results has not been sufficiently emphasized. Slightly less than 50 per cent. of severe cases were maintained under adequate control by long-term therapy, whereas the disease was satisfactorily suppressed in 70 per cent. of moderately severe cases and in 92 per cent. of moderate or mild cases. Although some severe cases failed to respond adequately even to large doses of cortisone, the chief detriment to good results was the intervention of adverse hormonal reactions. These developed at some time during the course of treatment in 40 per cent. of the patients. Whereas they were seldom of serious moment of themselves, their occurrence did influence the results. Their appearance, especially in severe cases, necessitated reduction of maintenance doses, sometimes to levels insufficient to provide desirable degrees of control of the rheumatic manifestations.

Adverse effects developed with much greater frequency when large doses of cortisone were employed. They rarely occurred with doses of 62-5 mg. a day or less, and in general their incidence was greater as larger doses of cortisone were used. The unwanted effects therefore were met most commonly during the early phase of suppressive therapy and in severe cases which required large maintenance doses.

The incidence of adverse reactions did not increase appreciably with prolongation of therapy. In our preliminary report given last year on uninterrupted administration for periods up to 4 months, the incidence was 35, 7 per cent. This compares favourably with the present incidence of 40 per cent. for periods up to 15 months. We believe that this surprising similarity is due to the fact that smaller maintenance doses have been continued in most patients.

Like others, we have tried to determine the rate of adrenal functional return following prolonged therapy. Cortisone was withdrawn in eleven of our patients who had been treated uninterruptedly
for periods ranging from 8 to 14 months. During therapy there was evidence of depressed function in each case, but after withdrawal values for urinary steroids and the eosinophil response to ACTH returned to normal. The rate of recovery from these tests was variable; for the eosinopenic response to ACTH, for example, recovery occurred within 10 days at one extreme and after 90 days at the other.

**DR. CURRIER MCEWEN (New York):** These presentations represent an extremely commendable and conservative attitude, but I think that they might be interpreted too pessimistically. The hope at the beginning that these hormones might lead to cures was bound to be followed by disappointment when we found that such was not the case.

I should like to make two points. First, that we all have many patients who are tremendously better off because these hormones are available. Second, that although these hormones do not cure disease, they do accomplish much more than the mere suppression of symptoms, in that they appear also to suppress the "rheumatic inflammation". I believe, therefore, that we have a right to expect that the prolonged use of cortisone over a period of years may result in a better ultimate functional status of the joints than would otherwise be the case when the disease had become inactive.

**DR. RUSSELL L. CECIL (New York):** We, too, have been disappointed in the combination of gold therapy and hormone therapy. We had the idea that by combining the two treatments, we might perhaps prolong the remission, but it has not worked out that way in the small series of twenty-odd patients that we have been following in the New York Hospital.

I have been impressed with how differently people react to cortisone; some swear by the tablets, and some think the intramuscular method is much better. The personal factor is certainly very important. Dr. McCuen made a good point, too, that we are all disappointed because cortisone has not worked quite so wonderfully as we hoped; yet we all have patients who have been greatly helped by it, and I think we should not be too pessimistic about the future.

**DR. DONALD F. HILL (Tucson, Ariz.):** We have now had a large series of patients, some on cortisone over a year, some almost two years. In spite of holding these people in remission, in a certain percentage we have noticed the progression of the disease (by x-ray, by increased porosis of the bone, and by continued loss of cartilage), in spite of the fact that the patient remained fairly well symptomatically. In regard to the dosage, we found an extreme variation. Some required high dosages to maintain the remission but, like other workers, we have seen complications.

However, I have one patient who has required as much as 150 mg. a day. She started over a year ago on the conventional routine; we tried to reduce the dosage, but each time she would have a flare-up of symptoms; now for the last 6 months she has been out of my control, being able to buy cortisone herself, and she has insisted on taking 150 mg. a day, in spite of all the warnings. However, I have visited her to observe the effects and she still shows no bad effects or toxic symptoms.

One other feature is that so many of these patients complain of lassitude; their joints, they tell me, feel like rubber; they don't feel well; they are often depressed. You can't put your finger on anything; you examine them and find no sign of infection; the blood count, sedimentation rate, and so forth show no essential change. But very frequently I have found they have had some infection, exemplified by a low-grade fever. This is not always apparent at the clinic, but at home a noon or evening temperature is often discovered.

Some of these temperatures can be reduced by a course of antibiotics, and within a few days the patient will say he has a marvellous remission and feels much better without changing the dosage.

**DR. WILLIAM S. CLARK (Boston, Mass.):** Dr. Hill has mentioned a problem which we have been somewhat concerned with, namely the progression of the disease under the influence of cortisone, when the dosages used suppress merely the symptoms.

We have had a number of patients under long-term therapy, and in following the literal requirements of the American Rheumatism Association Criteria, we have not seen Grade I or II remissions. Although these patients are symptomatically better and even working, we have sometimes observed objective evidence of an increase in the severity of the disease. We have also seen x-ray evidence of progressive joint damage, and in three patients in whom we followed the synovial fluid serially, we found changes which would indicate an increase in the severity of the inflammatory process.

It disturbs us that we are making our patients feel better and making it possible for some to be up and living almost normal lives, while at the same time permitting damage to the joints which a few years ago we would have taken great pains to prevent.

I should like Dr. Freyberg and Dr. Slocumb to define what they consider satisfactory improvement, for in our opinion the improvement is nearly always mainly subjective, and to comment on the possible harmful effect of long-term cortisone therapy by masking symptoms of the disease.
ANNALS OF THE RHEUMATIC DISEASES

DR. C. STEWART GILLMOR (Kansas City, Mo): We have made a study of 46 patients, some for up to 14 months. They did not respond to any treatment other than with cortisone, with which we have had very good results.

We usually give 50 or 75 mg. daily, and 100 mg. in a very few cases. Many of this group would be bedridden to-day if they had not had cortisone.

I agree with Dr. Clark that the feeling of well-being is deceptive, and we caution our patients not to exercise too much merely because they feel well.

DR. J. J. BUNIM (New York): At Bellevue Hospital we treated two patients during an initial attack, and one during a recurrent attack, of acute rheumatic carditis with massive doses of cortisone or ACTH after it had become apparent that they were not responding satisfactorily to usual doses. It is the impression of our group that no significant ultimate benefit was gained by large-dose administration. The resurgence of rheumatic activity following withdrawal of therapy, the total duration of illness, and the residual structural damage were not more favourably affected by massive than by ordinary doses, as is illustrated by this Table.

TABLE
USE OF LARGE DOSAGE OF ACTH IN RHEUMATIC FEVER WITH CHRONIC ACTIVE CARDITIS (8 MONTHS)

<table>
<thead>
<tr>
<th>Time of Examination</th>
<th>Before Therapy</th>
<th>Course</th>
<th>Three Weeks after Course 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2*</td>
</tr>
<tr>
<td>Hormone</td>
<td>None</td>
<td>Cortisone</td>
<td>ACTH</td>
</tr>
<tr>
<td>Maximum daily dose</td>
<td>200</td>
<td>100</td>
<td>320</td>
</tr>
<tr>
<td>No. of days treated</td>
<td>27</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Total amount (mg.)</td>
<td>2,900</td>
<td>835</td>
<td>4,960</td>
</tr>
<tr>
<td>Temperature</td>
<td>103·8°</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Heart rate</td>
<td>140</td>
<td>110-120</td>
<td>116-124</td>
</tr>
<tr>
<td>Quality heart sounds</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Gallop heart sounds</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Murmurs</td>
<td>Apical S+D</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Cardiac enlargement</td>
<td>Moderate</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Present</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Positive</td>
<td>Negative†</td>
<td>Negative†</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>98 mm.</td>
<td>9 mm.</td>
<td>28 mm.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Active carditis</td>
<td>Carditis persists</td>
<td>Carditis persists</td>
</tr>
</tbody>
</table>

* Interval was 14 days between Course 1 and 2, and 32 days between Course 2 and 3.
† C-reactive protein reverted to strongly positive at end of each Course.

Although the systemic effects and laboratory manifestations of the disease were all suppressed during the various courses, and to a greater degree during the periods of massive dose administrations, nevertheless the end results were not satisfactory.

DR. DAVID H. KLING (Los Angeles, Calif.): The introduction of oral administration has made the long-range use of cortisone more accessible to many patients, but unfortunately it has also made proper control of dosage much harder. Many patients are apt to modify the dosage either upwards or downwards, depending on the latest magazine or newspaper article they or their relatives have read; when it becomes necessary to discontinue the drug, such patients often find another doctor or pharmacist who will supply the tablets. This situation urgently requires the inclusion of cortisone among the dangerous and habit-forming drugs because addiction has occurred in addition to serious side effects.

The initial dosage should be high enough (between 200 to 300 mg. daily) to achieve the maximum improvement in the shortest time. This permits a quick evaluation of the reversibility of the process and gives the victim a glorious respite from rheumatoid arthritis. How long this vacation may be extended, how soon and how much the dosage can be reduced, depends on the circumstances, especially on the reactions, encountered in a given case.
AMERICAN RHEUMATISM ASSOCIATION

Therefore the maintenance dosage varies from patient to patient from a few to 100 mg. or more daily and has to be adjusted from time to time.

The percentage of cases which can be maintained comfortably on low doses for prolonged periods depends on the composition of the material. If early, mild, and moderately severe cases are the most numerous the percentage will be high; it will be low if severe cases of long duration predominate.

Reduction of dosage below the level which gives definite amelioration defeats the objective of therapy. Where this becomes necessary, on account of reactions, complete suspension of the course of cortisone is the rational procedure.

Dr. Ward and his associates mentioned an increase of libido among the reactions, but this is an exception, for decrease in libido and potency during and for some time after cortisone therapy is the general rule.

DR. EDWARD F. ROSENBERG (Chicago, Ill.): During the past two years, I, like many other clinicians, have attempted to estimate the value of long-term administration of these hormones in rheumatoid arthritis. My attitude to-day is by no means pessimistic. Many disadvantageous side-effects and some accidents have been observed, but I consider this inevitable in view of the powerful action of these agents. The post-cortisone withdrawal syndrome is painful, and failure to obtain complete improvement is often distressing, but nevertheless, a long-continued administration of both cortisone and ACTH can often be successfully accomplished without evidence of toxicity or serious side-reactions.

A continued study of many dosage schemes is needed and we must continue to search for measures to supplement the effectiveness of these hormones.

Despite these unsolved problems, I feel no discouragement, and to me the future looks bright.

DR. DOUGLAS TAYLOR (Toronto, Canada): I should like to ask four questions:

First.—I know of one patient who, although under very careful control in hospital, with frequent "negative" x-rays of the chest, suddenly developed acute miliary tuberculosis while being treated with ACTH (and cortisone). I want to ask the doctors who presented these papers whether or not it has been their experience that tuberculosis is a dangerous complication; or whether or not they feel that our patient may have been an isolated exception.

Second.—I believe that the best way to relieve pain and prevent deformity in a joint is by the proper use of a splint, combined with heat and the correct type of graded exercise. I should like to know whether attention has been given to protecting involved joints by splinting or bandages.

Third.—We see in the public press accounts of arthritic patients who were "crippled" or "bedridden," but who got up and danced and climbed ladders after receiving cortisone. I should like to know what happens in such cases to those joints which have been partly destroyed in advanced rheumatoid arthritis. It seems to me that in joints with eroded cartilages, swollen synovial membranes, and distended capsules, much additional damage would be caused. Has any study been made of the effect of this unwanted physical activity upon the damaged joints?

Fourth.—This refers to a fact already mentioned, that a patient can get ACTH or cortisone outside his own doctor's control. Can a patient go into a drugstore in the U.S.A. and buy cortisone without a prescription? A few patients have told me that after they had received the drug from a doctor they felt so well that they bought it on their own from a drugstore, and continued to use it without supervision. I think this is a dangerous situation with a drug so powerful, and still in the experimental stages. I am interested to know what type of control there is, if any, of the public marketing of ACTH and cortisone in the United States.

DR. WILLIAM B. RAWLS (New York): I should like to emphasize Dr. McEwen's remark, that we should not fear to use cortisone and ACTH, or belittle their value until further information is available. I have had untoward reactions in the past and will most likely have some in the future, but this will not prevent my use of these compounds. I have tried to instill caution but not fear into those who prescribe them.

There are a good many untoward reactions that have not been fully explored in these papers, and I should like to report our experience and also the information obtained by questionnaire on thrombo-embolic phenomena occurring during the use of these compounds. In my series of 100 patients, two developed myocardial infarction, and one thrombophlebitis during therapy. There were eighty replies to the questionnaire, and several hundred cases reported, but the data was insufficient in all except 1,036 cases. Thrombo-embolic phenomena occurred in eighteen patients in this group.

At the spring meeting of the New York Rheumatism Association, Dr. Stuart W. Cosgriff
annals of the rheumatic diseases

reported the occurrence of 27 thrombo-embolic phenomena in 21 patients out of 450 treated. There were 1,586 cases in the combined series with 48 (3 per cent.) instances of thrombo-embolic phenomena.

I believe the present recommended dose schedule of 300 mg. the first day, 200 the second day and 100 daily thereafter is too large, particularly in those with hypertension and/or arteriosclerosis, and that it may produce troublesome side-reactions. I believe we should begin with smaller doses and that the maintenance dose should be as small as will enable the patient to carry on a useful life. One should not attempt to maintain these patients quite symptom-free. Our maintenance dose has ranged from 37.5 to 75 mg., being mostly about 37 mg. I do not think we should be afraid, but that we should use a little more caution and adapt the dose to the individual. I should be glad to hear from other members who have had similar experiences.

Dr. Robert Muller (New York): I should like to ask whether there is any difference in the withdrawal syndromes of cortisone and ACTH.

Dr. William D. Robinson (Ann Arbor, Mich.): I should like Dr. Freyberg to tell us a little more about the two patients who developed diabetes during treatment. Did they have glycosuria only or did they also have hypoglycaemia? Did they develop ketosis? Did the diabetes persist?

Dr. Smith (Youngtown, Ohio): Was a deliberate attempt made to regulate the sodium and potassium intake?

Dr. Hugo A. Freund (Detroit, Mich.): Is this paper not intended merely as a progress report? We are still at an early stage in this type of therapy, and what we are hearing to-day is a report of what has been done to date. I do not know if the speakers wish us to understand that, when all these various types of cases in many stages are thrown into one hopper, we are to draw general conclusions from their failure or progress?

I feel that we have lost sight of the intention of the first speakers, who are evaluating the use of the hormones rather than drawing any final conclusions.

Dr. Bayles: I agree, of course, that this is only a preliminary report on the use of high-dosage cortisone therapy.

In our experience with children with rheumatoid arthritis, 200 mg. cortisone daily is not high-dosage treatment. Our two children with Still's disease, who received 400 mg. cortisone daily for 21 days, have remained now in remission for 35 days after stopping treatment. I feel rather strongly that high-dosage cortisone therapy will be useful in acute or chronic rheumatic fever, and I am sure that Dr. Bunim would agree that, even though he gave large amounts of ACTH, it could not be said that this simulated high-dosage cortisone treatment. In using ACTH one can never be sure of the actual circulating 11-, 17-oxyosteroid level which is produced.

I should like to comment on Dr. Engleman's remarks on intravenous ACTH, in that patients receiving 500 mg. cortisone a day do not respond to 20 mg. ACTH given over an 8-hour period. It is possible that they would respond to a 24-hour ACTH intravenous infusion.

I agree with Dr. Clark and Dr. Taylor and the others who pointed out that in the proper treatment of arthritis we must not forget the fundamentals of rest and proper joint care, which were used to such great advantage before the days of ACTH and cortisone. Perhaps it would be well to invite Dr. Swaim or Dr. Kuhns to talk to this group next year on orthopaedic management and the use of plaster casts in the care of rheumatoid arthritic joints.

Dr. Freyberg: I feel that some of the discussion centred in a pessimistic interpretation of our paper. I did not wish to give that impression. We set out to evaluate a certain plan of prolonged treatment. A preliminary report was made a year ago, at which time there had been no opportunity of following up these cases. As the title indicates, to-day's report is, as Dr. Freund so well put it, a progress report. Its purpose is to relate what in our experience cortisone will do and not do. I will refer to this aspect again after answering some of the more specific questions.

Dr. Taylor asked about the effect of cortisone on tuberculosis. Everyone should be cautious not to treat a patient who has tuberculosis. There is abundant evidence to indicate that this disease may be unfavourably influenced.

There was a question whether the withdrawal syndrome after ACTH is similar to that after cortisone. Some patients have had similar withdrawal manifestations. We feel that the withdrawal syndrome is not simple prolonged hypo-adrenalism, but is largely due to changes in the connective tissue which has become dependent upon large amounts of cortisone. Thus, even after correction of hypo-adrenalism by the use of ACTH, the syndrome persists until the connective tissue metabolism readjusts itself.

Dr. Robinson asked about the diabetes seen in our patients. I want to emphasize that we
have seen diabetic changes in patients treated with cortisone in more than the two mentioned in this series. This complication has occurred in the early stages of cortisone treatment and the steroid has been discontinued; thus such patients are not included in the group of cases given prolonged treatment. However, we intentionally continued cortisone in two patients in order to study the metabolic changes. When the steroid was discontinued, the diabetes gradually subsided. We think that cortisone will change a latent to a manifest diabetes. However, we were surprised to find that ketosis did not occur, even though in one patient as much as 180 g. sugar was eliminated in the urine daily.

We did not attempt to prevent electrolyte changes; we wished to learn the incidence of such changes, so made frequent observations to study them. When they occurred, we attempted to correct or control them.

I believe I can best summarize the feelings of our research group by recalling to you that in January, 1950, I concluded a paper presented before the New York Academy of Medicine, with the statement that I did not share the pessimism of many investigators regarding the future of the clinical use of cortisone and ACTH in rheumatoid arthritis, but felt it was up to the physicians and the chemists to find out how to put these materials to safe and effective use. I still feel that not pessimism but conservatism is required—because of the limitations that these studies show.

Clinical investigators recognize potentialities of this agent for the benefit of rheumatoid arthritis. Never before has such a potent antirheumatic substance been available, but we need to know better how to use it.

Although we have been disappointed with some of our results, we are not discouraged from our search for satisfactory practical methods of treatment.

**Dr. Slocumb:** I agree with Dr. Freyberg’s closing remarks. Dr. Hartung mentioned 50 mg. cortisone daily as the top dose for many of his patients. I agree that 50 mg. is the highest daily dose well tolerated by many women in the menopausal or postmenopausal period and also by a few women who are menstruating regularly. However, most men will tolerate daily doses of 62.5 mg. or more without signs of hypercortisonism. For patients with rheumatoid arthritis, large initial doses of cortisone which will produce maximal desired effects rapidly are not necessary and are usually not desirable. It is distressing to hear of patients who after the first day or two of treatment with cortisone or ACTH become euphoric and have so much relief of symptoms that they jump out of bed and jump around the room; we know this euphoric state cannot be maintained for long without development of hypercortisonism, and the patients resent the loss of this exhilaration produced by reductions in dosage. Patients with marked osteoporosis run the risk of fractures during such stimulation.

Cortisone and ACTH cannot be expected to repair damage already done to affected joints, nor can they be expected to control symptoms from over-use of the damaged joints. When significant damage to joints is present, it is best to determine carefully how much of the disability is due to active rheumatoid arthritis and how much to mechanical injury. It is best to place the patient at rest in bed for 1 to 3 days to prevent the over-use of affected joints. Those that remain inflamed and are least affected by the period of rest should be watched carefully in determining the dosage of cortisone or ACTH.

There were several questions regarding libido during administration of cortisone. In our experience there were no instances of decreased libido with small suppressive doses of cortisone.

When small suppressive doses of cortisone were used, supplemental use of potassium salts was not necessary and seldom was it necessary to restrict the intake of sodium chloride.

**Dr. Hench:** This has been an interesting and instructive afternoon, providing what one might call a “shakedown” session. It is exactly what we must have and will continue to have for many years to come.

I hope no one will take offense at something I should like to say. Some who are now trying to use cortisone or ACTH as therapeutic agents, especially for chronic diseases such as rheumatoid arthritis, are, it seems to me, unduly disturbed by the difficulties of the moment. When the clinical result is excellent and no undesirable effects occur, the physician’s spirit rises: “These hormones are wonder drugs,” he says; but in the face of difficulties (when it is not yet possible by present methods of administration to find an adequate dose free of side-effects, or when relapses occur) he becomes prematurely discouraged.

We must not be over eager and impatient in this matter of developing a better, and perhaps a complete, understanding of the physiologic use of cortisone and ACTH, especially in chronic diseases. We lack the basic information to establish a truly physiologic method of administration.
ANNALS OF THE RHEUMATIC DISEASES

Those who are trying to develop, by trial and error and with concern for calculated risks, a reasonably safe and effective method of administration are to be encouraged. Their labours are so necessary, and have already been surprisingly fruitful.

But in contrast to the harassed "therapists" (whose responsibilities and feelings I share) are those whose objective is not so much a dosage-scheme for to-day, but a basic knowledge of the role of these and related hormones in the pathogenesis of rheumatic diseases. Such investigators, despite the practical pressures of the moment, must collect for us the vital information we now lack: How much endogenous cortisone and ACTH do normal persons develop in health and under stress? how do the peripheral tissues of normal persons or rheumatic patients metabolize endogenous or exogenous cortisone or ACTH?

It has taken many years to reach what might be called "first base", to be able to demonstrate at will the potential reversibility or "suppressibility" of some of these diseased states and to discover agents for the study of this phenomenon. One must not be discouraged if "home plate" has not yet been reached, for I am confident that it will be reached in time.


Twelve patients with malum coxae senile were treated with cortisone. The early and late therapeutic results of this group were reported.

Discussion.—DR. RUSSELL L. CECIL (New York): I have not had much experience with the treatment of osteo-arthritis with cortisone, but we have not limited our work to the hip, but have tried cortisone on osteo-arthritis in the knee and in two cases in the back. One patient who did particularly well was a woman of 72 or 73, who had always enjoyed good health. She took cortisone very well and derived much benefit as far as the hip was concerned, but suddenly developed chills, fever, and pyelitis, which had probably been latent, due to an old stone in the pelvis of her kidney. The interesting sequel was that the pyelitis quietened down, and that under treatment the patient became asymptomatic. However, we did not dare give her any more cortisone, and the hip again became very painful. Thereupon a very animated argument was started between the urologist, the orthopaedist, and the medical men, as to whether she should have a cup operation on her hip. It was finally decided to have the operation, and the result was excellent. She now has a painless mobile hip, and no trouble with the kidney.

DR. JOSEPH HOLLANDER (Philadelphia, Pa): We have treated eight patients with osteo-arthritis of the hip with cortisone. As in Dr. Boots' series, most of the patients were of the older age group. We have not been as fortunate as he in results, but we agree with the indications for cortisone therapy in this progressive disease.

In six of our eight cases, we obtained insufficient relief of pain after two weeks' intensive therapy to justify continuing the drug. The two patients who did derive significant relief have not been followed long enough to determine what the long-range effect will be.

We feel, therefore, that while cortisone is worth a trial in malum coxae, it is not the treatment of choice, but rather something to use in severe cases demanding desperate remedies.

DR. SOLOMON P. CARP (New York): Our findings in a similar study are in accord with those of Dr. Boots. We observed thirteen cases of advanced osteo-arthritis of the hip, the majority with bilateral involvement. Each had been studied by the orthopaedists and referred to us as serious and difficult problems. The complaints in all cases were severe pain, stiffness, and impairment of motion of the involved joints; x-ray films showed advanced degenerative changes and almost total loss of joint space.

With ACTH and cortisone treatment, ten of the thirteen showed considerable improvement, relief of pain, diminution of stiffness, and improved co-ordination of motion. All ten were able to move with greater facility and to perform such simple motions as walking up stairs and arising from a sitting position, but only two showed any significant change in the range of motion of the involved joints.


ACTH and cortisone were employed in the treatment of twelve patients of whom six manifested the complete shoulder-hand syndrome and six were classified as acute or
chronic incomplete shoulder-hand syndrome. In most instances small doses (40-60 mg. ACTH or 50-100 mg. cortisone daily for a period of 10 days to 2 weeks) led to good therapeutic results. In some cases pain and swelling were alleviated and normal motion of the extremity established within a few hours. Shoulder-hand syndromes following post-infarction states responded favourably. Once pain had subsided and increased motion had been established, physiotherapy was found useful.

Excellent results were observed in ten of the twelve patients, two experienced relief from pain but did not regain the full range of motion.

Discussion.—Dr. Sidney S. Berkowitz (New York): Our findings have been similar to Dr. Sigler’s. In eleven cases of reflex dystrophy of the upper extremity treated with cortisone and ACTH, the results compare favourably with those in patients treated with sympathetic nerve blocks. In fact, we observed good results with the use of the hormones in several cases who failed to respond to stellate ganglion blocks. In our small series, somewhat larger initial doses were required for the first 5 to 10 days than those commonly needed in rheumatoid arthritis. So far our results have been impressive, and certainly warrant further study.


Fourteen cases with chronic symptoms refractory to treatment who were given ACTH and cortisone are considered in three groups:

(1) Eleven treated with these compounds without manipulation; effective treatment in six.
(2) Three of five cases in Group 1 who were unresponsive to the steroids, were subjected to manipulation and the administration of ACTH or cortisone was continued; treatment completely effective in one.
(3) Three received the steroid for the first time after manipulation had been carried out; great improvement and recovery in two.

Nine of the fourteen patients were greatly improved or recovered completely. Maintenance doses were required for a limited time to overcome recurrence of symptoms during attempted rest periods. The trend of responsiveness of periarthritis of the shoulder to ACTH and cortisone, without and with manipulation, suggests that further investigation would be worth while.

Discussion.—Dr. William D. Sicher (New York): One of the most difficult problems in evaluating reports of this type is the interpretation of the other man’s standards and criteria of what constitutes a serious or advanced case, and also of what constitutes a therapeutic response.

I have had the opportunity of following many of the patients included in the series just reported by Dr. Ehrlich, and should like to sketch one of these briefly:

This patient is a woman who began to develop pain and disability in the left shoulder late in 1948. Within a few weeks her pain was almost constant and the range of motion was limited to 10 or 15 per cent. of normal. During the next year she was seen by at least six physicians of various specialties. Treatment included physical medicine, x-ray therapy, local injections at trigger points with alcohol and iodine, other injections at trigger points with procaine hydrochloride, brachial plexus blocks, and several manipulations of the shoulder joint under anaesthesia.

After admission to hospital the patient’s condition deteriorated, until she was taking five to six doses of demerol each day. Within 2 to 3 hours of the change from placebos to cortisone, which was carried out successfully without her knowledge, the use of demerol was cut in half. Within a week from starting the cortisone, the demerol had been voluntarily discontinued and function at the left shoulder was rapidly returning toward normal. Within three to four weeks function was almost complete and the patient was pain-free. Cortisone was discontinued shortly thereafter, and the patient has remained well since then. That was almost a year ago.

There were other cases of this general nature in the series just described, and I believe this is what Dr. Ehrlich referred to when he talked about advanced and serious problems.

It would seem that further observations on the effects of cortisone are well warranted in these non-rheumatoid states.

Dr. Henry H. Jordan (New York): The result of manipulation under general anaesthesia for periarthritis or adhesive capsulitis of the shoulder depends to a great extent on the surgeon’s
486 ANNALS OF THE RHEUMATIC DISEASES

 technique. Few, if any, recurrences of adhesions will be found after atraumatic manipulation, but adhesions are much more common when the emphasis is on force rather than on time. The use of cortisone to prevent the formation of adhesions after manipulation seems logical and should be tried whenever possible.

DR. NATHAN R. ABRAMS (Cincinnati, Ohio): My series is not large, but my five cases were considerably shorter in duration. All were treated within the first month of their illness with cortisone on an ambulatory basis. Of the five, one showed no improvement at any time; of the other four, one experienced great improvement and maintained it after the cessation of two weeks' therapy, but the other three promptly relapsed and later responded well to other methods, such as x-ray therapy and physical therapy. This seems to show that methods other than cortisone should be used in the early stages.

DR. STEINBROCKER: I should like to add that the proportion of early cases in Dr. Sigler's group was higher than in ours, so there will be some difference in our results. Nevertheless, our results coincided very much with his, the difference arising from the fact that all our cases but one were chronic, longstanding examples of the shoulder-hand syndrome.

DR. LYON LAPIN (Montreal, Quebec, Canada): Was any difference noted by the investigators of these cases between those in which calcium was found by x-ray and those in which no calcium was found. As I understand it, Dr. Ehrlich's cases were all ones in which calcium was not seen.

DR. JOHN W. SIGLER (Detroit, Mich): Four of our patients had calcification, but there was only one case of periartithris that had calcification in the involved side.

DR. STEINBROCKER: None of Dr. Ehrlich's cases of periartithris showed calcification.


Lymphadenopathy is frequently encountered in patients with rheumatoid arthritis. Lymphatic system involvement is an integral part of the pathology of Still's disease and may be found in Felty's syndrome. Lymph-node biopsies in a series of patients with rheumatoid arthritis revealed pathological evidence of giant follicular hyperplasia; in some instances this was accompanied by fusion of lymph follicles, a criterion considered to be one of the characteristics of malignancy. Other patients showed follicular hyperplasia not of the giant variety. Serial lymph-node sections in instances of non-specific follicular hyperplasia and true giant follicular lymphoblastoma were compared with similar material from our series of patients with rheumatoid arthritis. While the period of clinical observation of these patients is too short to permit a definitive statement as to the true nature of the lymph-node lesions observed, it is our tentative conclusion that the histologic picture of giant follicular lymphoma (Brill-Symmers disease) may be simulated by the lymph-node lesions found in some cases of rheumatoid arthritis.

Discussion.—DR. WALLACE GRAHAM (Toronto, Canada): In 1948, two of our patients with severe rheumatoid arthritis were found to have unusual enlargement of lymphatic glands:

(1) In a male aged 42, some were the size of a small walnut. The biopsy was reported as typical of giant follicular lymphoblastoma.

The differentiation between cortex and medulla no longer exists and a good proportion of the glandular tissue is composed of huge hyperplastic lymphoid follicles with greatly expanded germinal centres with a thin compressed rim of lymphocytes surrounding them. Within the germinal centres mitotic figures are fairly numerous, etc.

A synovial biopsy from the knee revealed the usual picture of rheumatoid arthritis. After deep x-ray therapy the glands temporarily diminished in size. In 1950, biopsy of the glands was again carried out before and after the administration of cortisone. After 3 gm. cortone over 20 days the glands had almost completely disappeared. After cortisone, a large portion of the medulla was found to be replaced by fat. Germinal centres were numerous but small. The biopsy was reported as chronic lymphadenitis.

(2) A male, aged 38, presented a similar picture; the first biopsy was reported as giant follicular lymphoblastoma, and a synovial biopsy from the knee showed no significant lesion. This patient developed a tumour in association with a peroneal tendon. This also was non-malignant. A second biopsy of a gland in September, 1950, was reported as hyperplasia of a lymph node.

Both patients have now been under observation for three years and have shown no sign of malignancy. We feel that these glands represent an unusual hyperplasia in rheumatoid arthritis,
but should agree with Dr. Motulsky that the histologic picture of giant follicular lymphoma may be simulated by the lymph-node lesions found in some cases of rheumatoid arthritis.


Gross pathological changes were observed in the arthritides; the material came from the collection of skeletal remains in the Department of Anthropology of the Smithsonian Institution, Washington, D.C. The specimens selected were carefully studied, photographed, and X-rayed. Various stages in the calcification of the ligaments of the spine were presented, with examples of complete fusion of the spine, considered to be the end result of an ankylosing type of arthritis of the spine. Degenerative changes with hypertrophic spur formation of the various joints were illustrated. The antiquity of the various types of arthritis was shown in a fused cervical spine from the 12th Egyptian Dynasty (about 2000 B.C.) interpreted as a Marie-Strümpell arthritis. Specimens showed arthritic changes secondary to trauma, postural habits, developmental conditions such as coxa vara, and slipped femoral epiphyses.

**Discussion.** — Dr. Darrell C. Crain, Jr. (Washington, D.C.): This work deserves commendation from the purely physical aspect. The various museums in Washington contain more dried bones than ever Ezekiel saw in his famous vision. Dr. Tobin is the first who has tried to sort them and to bring some order out of chaos. It has been a tremendous physical task and he deserves the highest praise for the amount of time he has spent on this work.

Little of the material available in the various medical museums is properly catalogued, and little work has been done on the subject in recent years, Dr. Douglas Collins’s book being about the only up-to-date study, but work of this sort is essential for a clear understanding of the basic mechanism in the arthritides, and Dr. Tobin and Dr. Stewart have made a valuable contribution.

Dr. Edward F. Rosenberg (Chicago, Ill.): There is much to be learned from the study of bone specimens, and I hope this work will continue. I should like to call attention to a particular field of study in relation to the pathology of rheumatic diseases, the problem of rheumatoid sacro-ileitis. Clinicians daily observe progressive destructive changes in roentgenograms from patients with rheumatoid spondylitis, but the literature contains no information on the histological nature of these lesions. I hope that the studies described to-day will, as they are continued, throw some light on this subject.

Dr. Tobin: These specimens are quite old and are usually devoid of any soft tissue. Only the mummy specimens show any soft tissue, and even in these it is very difficult to make any study of the changes in the soft tissues.

I regret that time does not permit me to show additional specimens illustrating arthritic changes in the sacro-iliac joint, hip, and knees. Our paper is merely an introduction to this interesting subject. We have at the Smithsonian Institution approximately 20,000 skeletons from various geological and anthropological periods up to the present day, and so far, we have dusted off, so to speak, only the first row in the first room.

**Effects of Some 11-Desoxysteroids in Rheumatoid Arthritis.** By William S. Clark, Henrik O. Tonning, Joseph A. Blais, and Walter Bauer, Boston, Mass.

Forty-five patients received the following 11-desoxysteroids:

- desoxycorticosterone
- "saturated" desoxycorticosterone
- pregnenolone
- 16-dehydropregnenolone
- $\Delta^4$-pregnen-3-(b)
- 21-diol-20-one
- 21-propionate
- testosterone
- dehydroisoandrosterone
- progesterone
- premarin
- estradiol benzoate
- cortisone

In one patient, mineral and nitrogen balances were determined during the administration of testosterone, desoxycorticosterone, and cortisone—singly, together, and in binary combinations.

None of the steroids exhibited a significant antirheumatic effect in the dosages used. The mild subjective and objective improvement observed in some patients was no greater
ANNALS OF THE RHEUMATIC DISEASES

than that noted during the administration of placebos. In all cases the therapeutic results were classified as Grade IV (Steinbrocker).

Desoxycorticosterone and testosterone did not quantitatively or qualitatively alter the antirheumatic effects of cortisone, although testosterone counteracted its effect on protein metabolism. Desoxycorticosterone had no adverse effect on the arthritis even in the presence of considerable salt retention.

These observations further suggest that only carbohydrate active corticosteroids are capable of suppressing rheumatoid arthritis, and they indicate that the antirheumatic effect of cortisone cannot be altered by desoxycorticosterone and/or testosterone.

Discussion.—Dr. Howard F. Polley (Rochester, Minn.): Among the group of steroid substances chemically related to cortisone which we have tested at the clinic were six 11-desoxysteroid preparations.* Further data concerning three of these (desoxycorticosterone, \( \Delta^1 \)-pregnenolone, and 21-acetoxypregnenolone), are included in Dr. Clark’s report. Our results were similar to those which he has reported.

The other 11-desoxysteroid preparations which we tried were 11-desoxycortisone (also known as substance S of Reichstein), 17-hydroxyprogesterone, and pregnenetriolone acetate. None of these preparations revealed any antirheumatic activity.

I concur with Dr. Clark’s conclusions, that the 11-desoxysteroids are without antirheumatic activity in so far as we know how to use them at the present time.

Dr. William K. Ishmael (Oklahoma City, Okla.): Our preliminary report on the use of testosterone in rheumatoid arthritis was published in September, 1949; follow-up reports were made to the American Rheumatism Association in 1950, and again at the Steroid Conference in Mexico City in January, 1951.

Of the 124 patients who have received large doses of testosterone, approximately one-half have received it for 2 years, and approximately one-half for about 18 months.

At this time, 71 patients (57 per cent.) are still in Grade II remission. In addition to the Steinbrocker classification, we now require at least one year before we give an opinion on the final effects of any substance which is being tested. The above-mentioned 71 patients do not include eight women who were responding satisfactorily, but in whom the testosterone had to be discontinued because of undesirable side-effects.

After observing the effects of testosterone for this period of time, we have again concluded that this drug has no specific action against the inflammatory joint lesion, but is non-specific, exerting beneficial effects through a generalized metabolic influence. However, until a more specific substance has been developed, testosterone will have a place in the management of certain patients with rheumatoid arthritis.

Dr. William D. Robinson (Ann Arbor, Mich.): I should like to support Dr. Clark’s contention that rheumatoid arthritis is not characterized by an adrenal steroid with excessive salt and water activity. The best means of testing for mineralocorticoid activity is to determine the concentration of electrolytes in the sweat. Using as standards the test methods worked out by Dr. Jerome Conn, we applied this test to rheumatoid arthritis. We found that the sweat concentration covered a wide range, and in no case fell within the limits showing hyperadrenalinism, such as Cushing’s disease or adrenocortical tumour.

With respect to the antirheumatic effect of the adrenal steroid, I must add an observation which somewhat complicates the picture. We have done some preliminary work with one hormone having definite carbohydrate activity, namely, corticosterone, Kendall’s Compound B; we were unable to demonstrate any antirheumatic effect.

Dr. William R. Merchant (Washington, D.C.): Dr. Clark stated that testosterone will inhibit or prevent the alteration of protein metabolism without changing the antirheumatic effect. Does he use the term “protein metabolism” alone to refer to the nitrogen-balance studies presented, or does this include albumin/globulin alterations? If albumin/globulin studies were included, what methods were used?

Dr. John W. Gray (Newark, N.J.): We treated 60 patients with progesterone, giving 200 to 400 mg. intramuscularly daily for 1 to 2 months; 45 showed objective improvement, many complete reversals simulating those from the use of cortisone. They all relapsed when progesterone was discontinued. Then we tried 1,000 mg. orally daily for 1 to 2 months with no result. The

disadvantages of progesterone therapy are pain at the site of injection and withdrawal bleeding in pre-menopausal women.

We treated 36 patients with pregnenolone, four of whom improved but only subjectively.

DR. W. PAUL HOLBROOK (Tucson, Ariz.): One thing must be said in talking of these substances and various other steroids. We have all been guilty of running screening tests on these wholly insoluble substances, such as pregnenolone, when we have no evidence that they are absorbed either by injection or by way of the gastro-intestinal tract.

I believe that before we say that these steroids do or do not possess antirheumatic qualities, we ought to devise some method of determining whether these ordinarily insoluble substances are absorbed.

DR. J. J. BUNIM (New York): We studied the effects of desoxycorticosterone acetate on a child with Still's disease who responded very well but manifested the diabetogenic effect of cortisone. We desired to see whether the administration of desoxycorticosterone acetate would
(a) have an antirheumatic effect like cortisone,
(b) intensify the rheumatic disease,
(c) have no effect on the arthritis one way or another (as Dr. Clark reported).

Furthermore, we wanted to know whether DOCA would inhibit the diabetic effect of cortisone.

It was found that DOCA did not affect the arthritis either way, and it did not inhibit the diabetogenic effect of cortisone, but insulin readily brought the glycosuria and hyperglycaemia under control.

DR. CLARK: The ability of testosterone favourably to alter the nitrogen-losing effect of cortisone was first reported by Sprague, and our work merely confirms his.

The question of corticosterone interests me very much. If one examines carefully the evidence that carbohydrate activity is disassociated from antirheumatic activity, one finds it inconclusive. I think the studies with corticosterone from Ann Arbor offer the best evidence that carbohydrate activity is not always associated with anti-inflammatory effects. Our point was that all steroids known to suppress the arthritis have carbohydrate activity.

I agree entirely with Dr. Holbrook's comments. I think it is a very important point that if there is an antirheumatic hormone that does not have these metabolic effects, we want to know it, for it offers considerable hope in the management of the patient.

I also agree with Dr. Holbrook that we have no way of knowing whether these hormones remain in the gluteus muscles for months or are excreted in the faeces when given by mouth.

We have not shown that Dr. Selye's hypothesis is completely wrong, and I think it would be unwise to discard it. We have only indicated that if there is a pituitary hormone producing hormones pathogenic to connective tissue, it does not operate through an electrolyte effect. The remainder of the hypothesis, that there can be a pituitary substance now considered to be growth hormone which can be pathogenic to connective tissue, has not been disproved.

**Joint and Muscle Manifestations of Periarteritis Nodosa. By EDWARD W. LOWMAN, New York.**

Forty-three cases of periarteritis nodosa have been reviewed and joint and muscle manifestations evaluated. In thirty (70 per cent.) of the cases, muscle and joint symptoms were the early complaints; in only four cases, however, was there objective evidence of synovial involvement and in no case was joint involvement a major aspect of the clinical picture. Histological study of synovia showed arterial involvement identical to that seen elsewhere in the disease, with spotty synovial change secondary and proportionate to arterial involvement.

Muscle tenderness and aching were common early manifestations, but in only one case were symptoms suggestive of fibrositis, the muscle symptoms being worse with activity and better with rest. In nineteen there was progression to frank peripheral neuritis.

**Discussion.—**DR. WILLIAM K. ISHMAEL (Oklahoma City, Okla.): It might be interesting to comment on the preliminary diagnoses made on our last three patients with periarteritis nodosa. The first was diagnosed as gouty arthritis, the second as rheumatic fever, and the third as chronic rheumatoid arthritis. Biopsies proved them all to be periarteritis nodosa, which certainly illustrates the variable joint picture. One of these patients who has received ACTH intermittently for 1 year, is still alive.
Postpartum Plasma in Rheumatoid Arthritis and in Patients resistant to Cortisone and ACTH. By Louis W. Granirer, New York, N.Y.

In 1949 it was first reported from our clinic that a sustained remission can be produced in rheumatoid arthritis by the administration of suitable amounts of postpartum plasma. The remission produced is characterized by an improved sense of well being, brighter mental outlook, increased appetite, amelioration of joint symptoms, gain in weight, and restoration to normal of the microcytic anaemia and albumin/globulin ratio. In general, the characteristic response was a striking clinical improvement. There have been no toxic effects and in over 1,000 postpartum-plasma transfusions to date there have been no cases of homologous serum hepatitis. The longest remission after cessation of therapy was 2 years and the shortest 6 weeks.

Discussion.—Dr. W. Paul Holbrook (Tucson, Ariz.): We have had no experience with postpartum plasma, but we have done some pregnancy blood transfusions. Although, in over 100 cases there appeared to be two or three fairly dramatic results, we discontinued this treatment, primarily because it adds no hope whatever to the ultimate treatment of the thousands of patients with rheumatoid arthritis, since there simply is not enough pregnancy blood available.

Dr. B. M. Norcross (Buffalo, N.Y.): Dr. Lockie and I were very interested in this procedure. We were able to collect postpartum plasma, according to the plan described by Dr. Granirer, and it was administered, in units of 250 ml. at weekly intervals, to six patients with active rheumatoid arthritis. There was no subjective or objective improvement in our patients after each had received a total of twelve infusions, and we were forced to discontinue administration of the postpartum plasma in one patient because of repeated allergic reactions which could not be prevented by antihistamine therapy.

Dr. Russell L. Cecil (New York): The great problem in the treatment of rheumatoid arthritis is relapses. I wish Dr. Granirer would tell us more about the percentage of relapses, just how severe they were, and how long they persisted.

Dr. J. J. Bunim (New York): Dr. Granirer mentioned eight patients who had unfavourable effects from ACTH and cortisone, and responded well to postpartum plasma. It would be of interest to know how many of the patients who failed to respond to postpartum plasma, responded subsequently to ACTH and cortisone.

I have observed two patients who failed to respond to sixteen transfusions of postpartum plasma, but who showed moderate improvement when ACTH or cortisone was administered.

Dr. John W. Gray (Newark, N.J.): I should like to ask Dr. Granirer his plan for obtaining large amounts of plasma. We have found it difficult, through lack of co-operation on the part of the obstetricians and lack of interest on the part of postpartum women. To get anything at all, we had to supply twice as much blood as we took away, and then the mother was frequently alarmed to find a transfusion being given; we found more of them were interested in a fancy fee than in transfusion. Unless there is more proof than we now have of some degree of permanent relief, it seems to me too difficult a problem in most communities to obtain sufficient quantities of postpartum plasma.

Dr. Granirer: We feel the same as Dr. Holbrook; that at present this is a somewhat difficult form of therapy, but no more than insulin in the early days. Whether pregnancy has more or less of the active substance cannot be determined at present. The premise was that during and after delivery there was a sharp increase in hormones which pregnancy might not always possess.

We expect 20 per cent. failures. How long will a patient stay in remission after treatment? Remissions varied from 3 weeks to 2 years. A patient in remission may require treatment every 3 weeks, every month, every 3 months, or at longer intervals.

Patients who do not respond to postpartum plasma therapy may do well with ACTH or cortisone; postpartum plasma is usually beneficial in cases resistant to ACTH or cortisone. We have found that 35 per cent. of patients in the obstetrical ward will donate blood.

Acute Soft Tissue Calcification of Joints other than the Shoulder. By James W. Miller, Robert W. Hanf, and John H. Walker, Seattle, Wash.

Calcification of soft tissue, otherwise known as peritendinitis calcarea, tendonitis calcarea, or "bursitis", may occur near many joints of the body. The most common site is adjacent to the shoulder joint, but many clinicians are not aware that acute soft
tissue calcification may occur in other areas. Specific therapy for this syndrome is so
dramatic that an accurate early diagnosis is of utmost importance.

Acute calcifications may also occur at the elbow, wrist, interphalangeal joints of the
hand and foot, hip joint, knee, and ankle. We are reporting a series of 31 cases encoun-
tered between 1943 and 1950, which have been adequately followed up; in the majority
the region of the elbow, wrist, and hip was affected, in the order mentioned. During
this same period, 389 cases of "subdeltoid bursitis" of the shoulder were treated; these
were mostly acute with demonstrable calcification.

The pathology, symptoms and signs, and treatment of these lesions was discussed. Judicious x-ray therapy was considered the best method of management.

Discussion.—DR. GEORGE G. HAYDU (New York): Our experience is very much like that
just reported. I should like to call attention to the period that precedes tissue calcification; you
often find a period of mild complaint and undue stress in the areas of the tendons; inflammation
often occurs before calcification, and also, at times, long after x-ray therapy. It is well to treat
the underlying process in order to prevent any further recurrence.

DR. RUSSELL L. CECIL (New York): I had a friendly argument the other day with an orthopaedic
colleague, who insisted that they had decided, after years of observation, that x-ray therapy had
no value in the treatment of these self-limiting bursal conditions in the shoulder. I have always
felt that x-ray therapy was valuable in acute bursitis of the shoulder and other joints, but the
orthopaedist insisted that the radiologists in his hospital were equally convinced that we were
decieving ourselves in using x-ray therapy on the shoulder; he thought that the shoulder would
get well in a few days anyway, and that we were only wasting our time.

DR. OTTO STEINBROCKER (New York): I am inclined to agree with Dr. Miller. I think, however,
that the great value of local infiltration of procaine or a related substance, or the two-needle
irrigation of the acute calcification, is a valuable procedure that should not be dismissed too lightly.
Under ordinary circumstances the most practical procedure, according to our experience in these
conditions, is radiation therapy, but when x-ray treatment is not available the infiltration of pro-
caine or two-needle irrigation is a valuable technique to dispose of the symptoms and the calcium.
They have given us at least as high a proportion of good results as radiation therapy, and have
succeeded in some instances when radiation failed.

It is important to appreciate that in what we classify separately as hyperacute, acute, and
chronic conditions, the indications are somewhat different. The patient with a hyperacute
calcific tendinitis cannot tolerate irrigation or needling while conscious. Such a patient is in too
great pain and the local signs are too sensitive and extensive for such a procedure without a simple
general anaesthetic, such as a barbiturate intravenously. Usually an injection of morphine or
demerol will be satisfactory for needling a merely acute disorder in an ambulatory patient. A
chronic condition is not quite as effectively treated, because the chronic symptoms represent a more
complex problem, and a calcific deposit in the chronic involvement is merely a roentgenologic
sign which may divert us from the true source of the symptoms.

DR. DARRELL C. CRAIN, JR. (Washington, D.C.): Those of you who have read the Rheumatism
Reviews will recall that the last Review mentioned that more confusion surrounds the painful
shoulder than any other subject, but I think we are beginning to sort out that confusion. The
condition discussed by Dr. Miller is certainly analogous to the condition of calcific deposits in the
tendons of the shoulder. I should like to suggest that the term "calcaneous tendinitis" or
"calcific tendinitis" be used; it is a simple descriptive term, and one which could be readily adopted
for the condition in or around any joint.

As regards treatment, I agree with Dr. Miller and should like to stress the importance of early
x-ray therapy. In contrast to Dr. Steinbrocker's experience, my experience with needling has been
somewhat disappointing. In the early cases, when needling may be successful, it is often
too painful to be tolerated, and x-ray therapy is practically always successful; later, when the
deposit is harder, needling may be of very little benefit and may serve to irritate the condition.

DR. HOWARD F. POLLEY (Rochester, Minn.): I should like to ask Dr. Miller whether he thinks
the large calcium formations accumulate within the brief period that the symptoms come on.

DR. MILLER: I am an orthopaedic surgeon myself, and when I develop an acute calcification
associated with a joint, I shall choose to have x-ray therapy. I have confined my remarks this
morning to acute calcifications associated with joints other than the shoulder. I did that because
this disease is self-limiting, while in the similar shoulder lesions, where I am sure the pathology
is the same, there is often some residual periartthritis or chronic calcification with symptoms. Regarding the rapidity with which these accumulations appear, it is my opinion that they are frequently present and asymptomatic. Some inadvertent act, such as normal use or over-use of the part, aggravates the situation and the pain arises from mobilization of the calcium. This was Codman's concept of the disease. In most cases, though possibly not all, it has been there quiescent for some time. This theory is supported by the fact that in routine x-rays we often see calcific deposits that are asymptomatic.

**Sequela of Adult Rheumatic Fever.** By Ephraim P. Engleman, Leo Hollister, and Felix Kolb, San Francisco, Calif.

This report is based on a 6-year follow-up study of 137 unselected veterans who had rheumatic fever in World War II and now reside in the Pacific Coast area. This is the first known study of its kind. Half of the patients had been seen during the war by one of us (E.P.E.). Treatment of the service attacks had been limited to bed-rest and salicylates. The follow-up studies included physical examination and electrocardiographic x-ray, bacteriologic, psychiatric, and social surveys.

The incidence of recurrences in the past 6 years was low (11 per cent.). Nevertheless, two-thirds of the group experienced unexplained recurrent arthralgia. No instance of so-called "secondary" rheumatoid arthritis of the peripheral joints was seen. However, routine sacro-iliac x rays established the diagnosis of rheumatoid spondylitis in three patients with previous bona fide rheumatic fever.

Residual heart disease was seen in only 31 patients (22.6 per cent.), all of whom had had carditis during their service attack. With rare exception, cardiac findings were identical with those noted 6 years previously at the termination of their service attack, an observation of prognostic significance.

80 per cent. were leading normal lives, and the remainder showed only slight restriction in physical activity. These and other observations emphasize the favourable outlook of conservatively treated rheumatic fever in the adult.

**Discussion.**—Dr. Currier McEwen (New York): In a study of some children and adults reported some years ago by Dr. De Lilee, Dr. Dodge, and myself, the incidence of cardiac involvement was noted in relation to the age at which the rheumatic attacks occurred. We divided the patients in two distinct groups: under 12 and over 25 years of age.

There were 78 children with first attacks of rheumatic fever, of whom 46 showed definite evidence of carditis during the attack, and 28 per cent. showed persistent cardiac damage in follow-up. Among 67 adult patients with first attacks of rheumatic fever, 30 per cent. showed definite evidence of carditis during the attack, but only 7 per cent. showed persistent cardiac damage in follow-up. These figures bear out what Dr. Engleman has just reported. In fact our figures are even more optimistic for the adults than his.

Dr. Thomas McP. Brown (Washington, D.C.): Many of us have awaited with great interest the results of follow-up studies of these Army rheumatic fever patients, and this is our first opportunity of learning the course of adult rheumatic fever in a large number of patients followed for a significant period of time.

Dr. Swift used to comment that the arthralgias developing in adults who have had rheumatic fever in childhood did not necessarily represent a reactivation of the disease in the usual sense. He would not advise bed rest, was not concerned about carditis, and noted that these cases did well on salicylates. This supports Dr. Engleman's findings.

I should like to ask Dr. Engleman several questions: What was the streptococccic relationship with the onset of rheumatic fever in his adult group? Was it the same as in the child? What is his impression regarding dyspnœa? What was that due to? Was it an important symptom?

Dr. Charley J. Smyth (Denver, Col.): As you know, the incidence of rheumatic fever in the troops is still quite high, and during the past winter, at the Lowry Air Force Base, we have had the opportunity of collaborating in the study of some 31 young men who are in training there.

The six-year follow-up of men who had acute rheumatic fever during the last war will serve as a yardstick for future study, because they are now receiving carefully controlled courses of ACTH. ACTH was given intramuscularly in fourteen of these patients, and in sixteen it was given by intravenous slow drip for one week and intramuscularly for the next 7 weeks.
The Air Force is greatly concerned about this problem, and I think that Dr. Engleman's observations will enable us to measure what might be accomplished in treating this first or monophasic attack of rheumatic fever in these young adults without the use of hormones.

DR. HOWARD C. COGGESHALL (Dallas, Texas): I have had occasion to follow some of these patients through the Veterans' Administration, and I should like to raise one point. The adults with what was apparently rheumatic fever frequently have many muscular symptoms. Whether this is a variation common to adults, or whether it is a characteristic of veterans, I am not sure, but there is a great correlation between compensation and continued symptoms. Even though you find no evidence of heart disease, many of them will still not admit to being completely symptom-free. I think the problem of compensation always makes it difficult to evaluate veterans unless you have objective evidence of definite disease.

DR. ENGLEMAN: Dr. Brown asked about the incidence of streptococcal infection in adults. I must emphasize that this is a follow-up study and that we have no data concerning streptococcal infection before the onset of rheumatic disease. I think, in general, that there was a fairly good relationship between streptococcal infection and the onset of the initial attack.

As far as the dyspnoea was concerned, we felt this was a manifestation of cardic neurosis.

Dr. Coggeshall's point concerning the difficulty of the evaluation of the veteran who is receiving compensation is an excellent one. However, as far as arthralgia is concerned, we were impressed by the organic pattern. These patients were worse in the morning upon arising and were helped subjectively by aspirin, local heat, and by physical activity. We felt that most of these patients had genuine joint symptoms which were not satisfactorily explained.

**Effect of Benemid in Gouty Arthritis.** By BERNARD M. NORCROSS, L. MAXWELL LOCKIE, JOHN H. TALBOTT, and CHARLES BISHOP, Buffalo, N.Y.

Benemid was administered orally on several different dose schedules to a group of more than 25 patients. Medication was continued over a period of several months. The effects of Benemid upon carefully controlled blood urate observations, upon the frequency and severity of gouty attacks, and upon urate excretion, and its low toxicity was discussed.

In some patients, Benemid was used in conjunction with colchicine and salicylates, while in other gouty patients, it was the sole medicament employed. The effect of Benemid on uric acid metabolism in normal subjects was also mentioned.

It is our belief that Benemid is of value in the long-term control of the disturbed gouty metabolism, and may prevent or minimize the frequency and/or severity of attacks, as well as the complications of this disease.

**Discussion.—**DR. RICHARD T. SMITH (Philadelphia, Pa): We have had experience in fifteen patients with gouty arthritis, having treated them for a period of several months or more. When we first attempted to use Benemid, we used doses of two g. or more a day, and found some patients did not tolerate those doses so well. From experiences in using Benemid with penicillin, it was found that lower doses were successful when there was some renal impairment. Therefore, in gouty arthritis, we tried smaller doses, 0.5 g. daily for a week (one tablet), then increasing the dosage to 1 g. (two tablets) in divided doses thereafter.

Of the fifteen patients, three had chronic gouty arthritis and six were having increasingly frequent attacks. Nine of these patients had not been adequately controlled with acetylsalicylic acid and sodium bicarbonate, as evidenced by frequent attacks.

In eight of the fifteen patients attacks were precipitated by the therapy; none of these occurred during the first week, when they were receiving only 0.5 g. Benemid daily. The longest period of repeated attacks during the early stages of the Benemid therapy was 10 days. In only one of these patients was it very severe. The shortest period of increased joint difficulty was 3 days, and the average about 6 days.

Maintenance doses of colchicine were continued in four patients; in one of these no increased attacks occurred during the early Benemid therapy; in three there were some mild attacks with the maintenance dose.

Our patients have been warned in advance that they might anticipate some increased joint difficulty during the first few weeks of Benemid therapy. Expecting this, and having been instructed to take their colchicine, as they would for acute attacks in the past, they were well prepared in most instances for relief of their discomfort.
ANNALS OF THE RHEUMATIC DISEASES

We have also given sufficient sodium bicarbonate to produce alkalization of the urine, particularly to prevent the possibility of precipitation of urate crystals in the kidney.

We have permitted a liberal diet to the patients throughout treatment, particularly after the first 2 or 3 weeks for those having the greatest amount of difficulty. We had no means of predicting which patients would suffer attacks during the early stages of Benemid therapy, but there is a suggestion that we might expect increased attacks in those whose gouty arthritis had been more severe just before treatment was started.

It may be possible to prevent these increased attacks with the Benemid therapy by giving smaller doses for a longer period. This study we have not yet completed.

One fact is outstanding, that we have a substance apparently superior to anything we have used before as a uricosuric agent, and that with just one to four Benemid tablets a day, many gouty patients are permitted to live an almost normal life with little or no recurrent disability.

DR. LOCKIE: It should be emphasized that we are continually looking for something that will lower the blood uric acid or prevent attacks of gouty arthritis. Here is a substance which has been found to be useful, and relatively non-toxic, and, in Buffalo, it has not precipitated acute attacks of gouty arthritis. I am surprised that Dr. Richard Smith has had so many in his series in Philadelphia.

However, it must be remembered that we are using 0.5 to 1.0 g. twice a day, in conjunction with other means of treatment, except that the weekly administration of salicylates or cinchophen is omitted. It does not prevent the occurrence of acute attacks, nor does it replace colchicine. In the group we have studied, many patients have been followed for years, so that the pattern of attacks is well known, and it is felt fewer attacks of gouty arthritis have occurred.

DR. WILLIAM H. GOODSON (Kansas City, Mo): What is the effect of Benemid on acute gout and are there any complications?

DR. EPHRAIM P. ENGLEMAN (San Francisco, Calif.): What is its advantage over aspirin?

DR. NORCROSS: In our experience, 1 g. Benemid daily was not as effective as reported by Dr. Smith. We were not able to maintain the maximal reduction of serum urate with this dose unless considerable renal impairment was present. Because of the absence of toxicity, we have continued to use 2 g. daily in the majority of our patients.

Dr. Lockie answered the question about provocation of acute gouty arthritis by Benemid. We have not observed any significant incidence of acute attacks precipitated by Benemid therapy.

We believe that there has been a reduction in the number of attacks of gouty arthritis in this group, although some have had acute attacks after a year of Benemid administration. I think that much more time must elapse before we can make a definite evaluation.

Two patients who developed acute gouty arthritis during Benemid administration were not relieved by larger doses; we employed therapeutic courses of colchicine, and ACTH was used successfully in one patient.

The dosage of salicylates necessary to produce the same continued increase of urate excretion as that observed with Benemid has not been tolerated by many patients. Because there is also a rapid decrease in the salicylate effect on urate excretion with prolonged administration, we have used salicylates in the past on an intermittent, rather than on a continuous, schedule. We believe that Benemid is a better drug than the salicylates because it is not toxic and its effect on urate metabolism is prolonged indefinitely.

Panel Discussion

A panel discussion on "Difficulties and Complications in the Therapeutic Use of ACTH and Adrenocortical Steroids in the Rheumatic Diseases" was conducted by Dr. Philip S. Hench, Chairman, with Drs Edward W. Boland, W. Paul Holbrook, Charles Ragan, and William D. Robinson on the platform.

CHAIRMAN HENCH: Just a word before we start this panel discussion. The papers and discussions of yesterday show that the unjustified hopes and the unjustified fears concerning cortisone and ACTH are rapidly disappearing. The present status of cortisone and ACTH and their application to rheumatic and other diseases is somewhat analogous to the situation which would have occurred had insulin been discovered before we discovered methods for determining the sugar in blood or urine or knew anything about the metabolism of carbohydrates in the normal or the diabetic. Until methods...
have been developed whereby one can estimate the quantities of cortisone and ACTH present in blood or bodily tissues of normal and diseased persons, and until we have learned much more than we know now about the metabolism of these hormones, we can only use them therapeutically by a process of intelligent trial and error, by making mistakes and learning from them.

We will discuss first a few questions on rheumatic fever, and on gout, and then proceed to rheumatoid arthritis. The first question is this: How long must cortisone and ACTH be kept up in acute rheumatic fever?

DR. HOLBROOK: Many patients with acute rheumatic fever show complete subsidence of symptoms after receiving cortisone or ACTH for only a week or 10 days, but others do not. Therefore, in order to provide the maximum chance of preventing cardiac damage, we consistently give the hormones for 4 weeks.

CHAIRMAN: DR. May Wilson—who uses, as I think you know, one or the other hormone for only one week—told me this morning that her excellent results largely depend on the fact that she can get her "pedigreed" patients, already under general observation, very early, and can start treatment within the first 2 to 4 days of the attack. DR. Holbrook, have you any comment on Dr. May Wilson's plan?

DR. HOLBROOK: None, except that the recurrences that develop in some of our patients when treatment is discontinued at the end of a week seem to us more hazardous than the continuous administration of the hormones for a longer period.

CHAIRMAN: Is heart failure with oedema always a contraindication to the use of cortisone and ACTH in acute rheumatic fever?

DR. HOLBROOK: No, it is not always a contraindication. But it should be carefully borne in mind that low sodium intake, and other means of preventing the accumulation of electrolytes and fluid, should be used in acute rheumatic fever with heart failure.

CHAIRMAN: Do you use diuretics and salt restrictions routinely in rheumatic fever?

DR. HOLBROOK: Not unless heart failure is present.

CHAIRMAN: We will now turn to gout. Are cortisone and ACTH any better than colchicine? If so, which is the better, cortisone or ACTH?

DR. ROBINSON: I believe that colchicine, as it is customarily used, will take care of perhaps 90 per cent. of acute gouty attacks. For those patients who do not respond to colchicine, ACTH offers an excellent treatment. We believe that the dose of ACTH must be large, 100 mg. a day of a long-acting, or up to 200 mg. per day of short-acting, preparation. It must be combined with colchicine, and colchicine in maintenance doses (two to three tablets a day) should be continued for a while to prevent the occurrence of a "withdrawal attack". In our experience, cortisone has not been as satisfactory as ACTH in the treatment of acute gouty arthritis.

CHAIRMAN: Are cortisone and ACTH useful in chronic gouty arthritis?

DR. ROBINSON: I don't believe anyone has had enough experience to justify any statement.

DR. BOLAND: Our experience with cortisone and ACTH in the treatment of chronic gouty arthritis has been limited to a few cases. In general we are not convinced that these substances will produce persistent relief of chronic articular disability over long periods, and we are not sure that their uninterrupted use actually lessens the number of acute recurrent attacks. I agree with Dr. Robinson that ACTH is a good adjunctive measure if colchicine fails, but in the usual case of acute gouty arthritis we prefer colchicine to either cortisone or ACTH.

CHAIRMAN: Now we have a few general questions.

What about ACTH peptides? Are there any prospects for their synthesis in the near future? Will they be made effective and easier to use than now?

DR. RAGAN: It will be difficult to synthesize an ACTH peptide. These peptides have been found to be of rather high molecular weight, and in our experience so far, there has not been much difference between the peptides and whole ACTH.

CHAIRMAN: Should the use of cortisone and ACTH still be considered more or less experimental?
DR. RAGAN: I personally don't think so, but I do think that they should be used with considerable caution and conservatism. I don't think they should be considered experimental in the sense that you don't know what will happen. Their use is still "experimental" if one is considering what the results might be after a 5-year period.

DR. BOLAND: Regardless of how we feel about it, and irrespective of whether we think these hormones should be used only as experimental tools, the fact is that cortisone and ACTH are both on the market and are being employed as treatment agents. It is important, therefore, that we face this reality and strive to find, as quickly as possible, safe and effective methods of employing them in the practical management of patients.

DR. ROBINSON: My viewpoint coincides with those of Drs. Ragan and Boland. The ultimate place of these hormones in the practical management of arthritis, we certainly do not yet know, but I do believe that in the last two years we have been able to discredit some of the fears concerning them. It is also necessary to discredit some of the hopes, but we do know that a significant percentage of patients can be given these hormones safely and effectively for a considerable period.

CHAIRMAN: May I say a word. We have been using cortisone and ACTH at the Mayo Clinic mainly as tools for research, trying to find out, first of all, something about the reversibility of rheumatoid arthritis. That is still our main concern. But the many rheumatologists and other physicians who are now trying to develop a useful, if empiric, method of treatment, are making a splendid contribution. Physicians must try to find out to what extent these hormones can be used now as a safe and effective form of therapy as well as improved methods for their future use.

Next question: What are the chances that long-continued use of cortisone and ACTH will induce irreversible damage to the adrenals?

DR. HOLBROOK: The evidence is fairly clear now that after the prolonged administration of these hormones (e.g. after a year or more of cortisone) the adrenal recovers sooner or later, generally sooner.

DR. BOLAND: That is our belief also. As was stated yesterday, we have given cortisone uninterruptedly for periods up to 14 months and have then withdrawn it. After withdrawal, adrenal cortical function, as indicated by various tests, has recovered in every instance, although in one case it took the eosinophil response as long as 90 days to return to normal.

CHAIRMAN: We now pass on to the subject of rheumatoid arthritis. What are the most common side-effects you have encountered from the use of cortisone and ACTH in rheumatoid arthritis?

DR. HOLBROOK: The short-term usage of these hormones presents no particular problem as regards the development of side-effects, but after prolonged administration of cortisone and ACTH, about 50 per cent. of our patients have developed one or more of the following: round face, oedema, excessive mental stimulation, tachycardia, fatigue, dyspnoea, and so forth. But we do not necessarily stop the medication upon the appearance of any of these findings. In my opinion a daily record of the patient's weight is the best indication whether matters are progressing safely. Excessive gain in weight may be the first indication of trouble.

DR. RAGAN: One point that has not been mentioned much is the appetite of patients receiving the hormones. They consistently gain weight, even without retention of fluid, and it is difficult to keep their weight in reasonable bounds. This is one of our major difficulties, especially if the patient is a young girl who does not want to be a fat girl.

DR. BOLAND: It is our practice to limit the caloric intake as soon as the patient approaches an optimal body weight. Because cortisone and ACTH apparently increase the absorption and utilization of fats and cause increased appetite, it is very difficult to effect weight reduction during treatment if excessive gains have already been allowed.

DR. ROBINSON: The frequency and severity of these adverse manifestations is very definitely related to dosage, as was well brought out in the previous discussions. Sex and age are also important factors in the liability of patients to develop the common side-effects.

CHAIRMAN: Are the side-effects which may result from cortisone different from those which may result from ACTH?

DR. BOLAND: They are essentially the same, although in our experience retention of salt and water and arterial pressor effects are more prone to develop with ACTH than with cortisone.

CHAIRMAN: How often do you have to use special precautions (limitation of salt;
salt-free diet; diuretic) to prevent or control oedema? Do you use any of these routinely or not until oedema has developed?

Dr. Boland: One can go ahead with routine treatment until oedema occurs, and then restrict the intake of salt and/or administer saline or mercurial diuretics. We prefer, however, to place patients routinely on a salt-poor (not a salt-free) diet whenever large or relatively large doses of cortisone or ACTH are being used. This has been valuable during the early phases when large suppressive doses of cortisone or ACTH are employed, and by taking such precautions we believe that oedema is often prevented from occurring. In general, when maintenance doses larger than 50 mg. cortisone a day are being given, the intake of salt is routinely restricted; when this is done it is seldom necessary to resort to diuretics.

The appearance of oedema during treatment should not necessarily serve as an indication to stop cortisone. It is, however, an indication to institute the measure just described and/or to reduce the dose of the drug.

Chairman: What is the best way to prevent undesirable effects from cortisone or ACTH in rheumatoid arthritis? What should be one's general policy?

Dr. Ragan: It is best to undertreat rather than to overtreat the patients. Most of the undesirable results are directly related to excessive dosage. I do not yet know how to predict the development of major mental reactions, although some investigators believe that irritability in the patient is a danger signal.

Chairman: How much and what do you tell a rheumatoid patient before you begin to use cortisone or ACTH?

Dr. Holbrook: To begin with, I make it plain that the hormones are not per se a cure, and that other things are also useful. Once a decision has been made to use cortisone or ACTH, the patient must be prepared and willing to take it and able to afford it indefinitely. In my opinion, nothing is to be gained by short-time relief. My goal is to provide a significant amount of relief with a minimal dose. I aim not at the maximal degree of remission which maximal doses will provide but at the greatest improvement from the smallest dose.

Chairman: What are the absolute and the relative contraindications to the use of these hormones? Should they be used in the presence of tuberculosis, peptic ulcers, diabetes, psycho-neurosis, a positive Wassermann, amyloidosis, "abdominal pain", and so on?

Dr. Holbrook: There are only two conditions which I consider great contraindications—tuberculosis and diabetes. I am not yet willing to say that they are absolute contraindications if certain other precautionary measures are taken.

Dr. Boland: I cannot comment on tuberculosis because we have not observed reactivation of a pre-existing lesion in any of our cases, but I can give an opinion on diabetes. For a time glucose tolerance tests were done on every patient who was a candidate for cortisone. Only two patients with normal pretreatment tolerance curves have shown evidence of decreased tolerance to carbohydrates during treatment; in both of these the glycosuria was easily controlled with simple restriction of carbohydrate in the diet.

One of our first patients to receive cortisone was a diabetic whose disease was being controlled by diet and 10 units of insulin a day. Within 48 hours of starting cortisone there was a five-fold increase in the insulin requirement and this increase persisted throughout an 8-day period of treatment. However, the insulin requirements returned to the pre-cortisone level within 48 hours of discontinuing the drug. This indicates that although cortisone accentuated the diabetic state, this accentuation was temporary. Since that time we have treated three rheumatoid patients with pre-treatment latent or mild diabetes mellitus; each of them has received continuous cortisone therapy over a period of many months, and in each instance we were able to control the diabetes satisfactorily—in two by diet alone and in one with diet and moderate doses of insulin.

Mild or latent diabetes is thus not necessarily a contraindication to the use of cortisone, whereas more severe diabetes probably is. One must weight the relief to be obtained against the potential dangers. Knowing that any accentuation of the diabetes will be temporary, a cautious trial of cortisone in mild cases would seem justified.

Dr. Ragan: Latent or obvious tuberculosis is a contraindication. Drs. Knowlton and Perera have had experience with the treatment of Addison's disease and tuberculosis, and we agree with Dr. Thorne and Dr. J. S. L. Brown, that, if you make the organism euadrenal, tuberculosis may be controlled: but if, to achieve a beneficial effect, you have to produce hyperadrenalism, tuberculosis
is a real contraindication. We have had one case of tuberculosis in an Addisonian who has done extremely well on cortisone since we attempted to produce euadrenalism and not hyperadrenalism.

The second major contraindication is a history of psychosis. If a person has had a psychotic episode, we feel the chance of developing a second psychotic episode on cortisone is very great.

DR. ROBINSON: Most of the contraindications are relative. It is a matter of weighing what the patient has to gain against the possible difficulties, the potential response to other forms of treatment, and your own ability to regulate the complicating disease.

I am apprehensive about the use of these hormones in patients with a previous history of peptic ulcer, because I do not know how to detect an early reactivation of an ulcer under cortisone or ACTH, and because of the rapidity with which disastrous complications can occur.

CHAIRMAN: We have had a few rheumatoid patients who have had inactive duodenal ulcers, so far without any untoward effects. But we consider a peptic ulcer to be an important relative contraindication, and we watch such cases much more closely. Whether we use cortisone depends on the severity of the disease, and the risk is always explained to the patient.

DR. BOLAND: Within the past three months I have seen two patients in consultation who had developed convulsive seizures during ACTH therapy. Both patients had had typical epilepsy in the past and I would suggest that a history or epilepsy might serve as a contraindication.

CHAIRMAN: What is the incidence of rebound reactions after hormonal withdrawal?

DR. ROBINSON: Probably the best available figures are those which were presented by Dr. Freyberg. I believe that, of his 47 patients, five developed severe relapses after withdrawal of cortisone. Our experience has not been so extensive, but relapses can be severe, and they are likely to be a little more severe with sudden cessation of dosage, particularly of oral cortisone.

DR. HOLBROOK: I have found that cessation of oral cortisone is followed by exacerbations much more often than was reported. At least half of our rheumatoid patients developed a severe exacerbation when the oral cortisone was discontinued.

DR. BOLAND: We have seen more rebound relapses than Dr. Freyberg, less than Dr. Holbrook.

DR. RAGAN: We cannot be sure whether the withdrawal attacks represent a rebound or a natural progression of the disease, or whether the patient is worse than he would have been.

CHAIRMAN: How often do cortisone and ACTH lose their effect when dosage is unchanged? Does this happen more often or sooner with ACTH than with cortisone?

DR. RAGAN: I think that many so-called relapses are due to a natural progressive increase in the severity of the disease. Dr. Holbrook suspects that the thyroid has something to do with these exacerbations, and that secondary hypothyroidism sometimes develops, making the cortisone temporarily less effective. When rheumatic symptoms increase during the use of a previously satisfactory dose of cortisone or ACTH, we try to modify the severity of the disease, first by increasing the dose; secondly, by decreasing the physical and emotional activities of the patient.

CHAIRMAN: If a patient develops some intercurrent infection while on a maintenance dose, should one alter the dose? Should one take any special precautions?

DR. HOLBROOK: When a slight cold develops no alteration of the dose and no special precautions are needed. If a major infection develops, we do not alter the dose of the hormone but we may need to use antibiotics also. Sometimes during a course of hormone therapy an infectious process develops very insidiously and fails to give localizing symptoms. The patient may experience nothing but weakness, and, if you take the temperature faithfully, you may find a low-grade temperature. But if you give antibiotics to such a patient he will improve rapidly.

CHAIRMAN: If a rheumatoid patient has recovered from a mild stroke, are cortisone and ACTH safe, and which is safer?

DR. BOLAND: Again one must weigh the benefit against the danger. If the patient's arthritis is so crippling and so uncomfortable that life is miserable, and if his expectation of life is not too long anyway, one should consider employing these drugs cautiously. We have had three deaths during prolonged cortisone treatment—two from acute coronary thrombosis and one from a cerebrovascular accident. All of these occurrences were in older persons, and whether the increased physical activity made possible by the drug may have influenced the course of events or whether the episodes were coincidental we cannot be sure.

I should like to stress one complication which has been very disturbing to us and which has so far occurred only in elderly patients receiving large or relatively large doses. Three patients
developed spontaneous fractures during cortisone therapy; two of these were compression fractures of the lower dorsal spine and the other a fracture of a femoral neck. In view of the fact that spontaneous fractures are not uncommon in patients with Cushing's disease, we believe that this complication may be related to cortisone therapy—to us it appears likely that osseus demineralization may have been accelerated by the induced state of hypercortisolism. The possibility of this complication must be kept in mind in considering cortisone or ACTH therapy in older patients with evidences of skeletal osteoporosis from senility and from rheumatoid arthritis.

**CHAIRMAN:** Is thrombophlebitis ever a definite side-effect from cortisone or ACTH?

**DR. ROBINSON:** The occasional development of thrombophlebitis during or after the use of these hormones raises the question whether it is related to the treatment or is co- incidental. We have been somewhat concerned about this, because we had four cases of thrombophlebitis among our first thirty patients. In each instance, the thrombophlebitis developed when the dosage was being decreased or had just been discontinued. Two instances were in patients in whom thrombophlebitis might be expected, one being a recurrence at the site of a previous attack 2 years before. The other two instances were in young people and the circumstances were rather unusual.

We have heard some statistics at this meeting which place the incidence of thrombotic occurrences during hormonal therapy between 1.7 and 2.1 per cent. Has anyone any figures of the incidence of thrombophlebitis in rheumatoids who have not received cortisone or ACTH?

**CHAIRMAN:** When the members of the panel were talking about this last night, none had any statistics on the "natural occurrence" of thrombophlebitis among rheumatoid patients.

Among our early patients who received cortisone or ACTH, two developed thrombophlebitis when we were withdrawing or had just withdrawn cortisone, and we became somewhat concerned. Then we were about to begin giving cortisone to another patient on a Monday, but that particular patient developed thrombophlebitis on the Saturday before. So we do not know the final answer.

Next question: How often do cortisone and ACTH produce significant hypothyroidism?

**DR. ROBINSON:** That depends on how you define the term "significant." In our experience, some 85 per cent. of patients with rheumatoid arthritis on cortisone or ACTH have shown laboratory evidence of decreased thyroid function, as indicated by determinations of protein-bound iodine and the radio-active iodine uptake. Under ACTH and cortisone treatment, the basal metabolic rate is not reliable as an index of thyroid hypofunction.

In our experience, all the cases of elevation of blood cholesterol reported as a complication of prolonged treatment have been associated with evidences of hypothyroidism; the hypercholesterolaemia is corrected by the addition of desiccated thyroid. If it is asked from the practical viewpoint, how often is it necessary to add thyroid to maintain the clinical effectiveness of these hormones, I must reply that to date, we have seen no patient who required added thyroid to maintain the therapeutic effectiveness of cortisone. Others, however, have reported seeing such patients. We have observed four out of nineteen patients in whom thyroid supplementation was clearly necessary in order to maintain the therapeutic effect of ACTH, and in other patients, on either hormone, we have seen correction of minor clinical and laboratory aberrations.

**CHAIRMAN:** What symptoms first suggest an impending psychic reaction? If they appear, must one always stop the hormone?

**DR. RAGAN:** As I mentioned before, I think that evidences of over-stimulation, notably excessive mental activity, may suggest an impending psychic reaction.

The major psychopathic reactions that we have seen came as complete surprises. The electroencephalogram is of little value, since encephalographic abnormality may not be correlated with an abnormal mental reaction. If a patient develops a major psychosis, we certainly stop the hormone; but we do not know how to predict such a development.

**DR. HOLBROOK:** Nor do I know how to choose between the patients who will have psychic disturbances and those who won't. I think if the patient is watched closely, one will note that a mood of depression often precedes a major psychic reaction.

**DR. RAGAN:** How closely are you going to watch the patient?

**DR. HOLBROOK:** It is impossible to watch all of them closely. I agree with that. On the other hand, if you ask the patient to report his moods or changes in mood, you may get some warning.

**CHAIRMAN:** Assuming you are decreasing rather than increasing dosage, have you any comment on the time limit within which major psychic reactions are or are not likely to occur? If you have no psychic reaction within a few days or weeks, are you safe?
At present, therefore, we had patient accurate in Cortisone patient. Levels of (Bursitis) Tendinitis of ACTH and Effect Ganglion Injection Intra-Articular Emotional Background Pathology of Early Studies of Transmission of Pains of Effects Effect on Practical Importance of Rheumatoid Spondylitis 10, 255).

RAGAN: DR. BOLAND: Our climate in California is so happy, that we have had no such difficulties.
CHAIRMAN: Our psychiatrists have seen most of our patients and have done personality appraisals in many cases before we gave the hormones. Their reports have been gratifyingly accurate in telling us what sort of reaction we might meet in any nervous or unstable rheumatoid patient.

**Additional Papers**


*Peptidase Levels in Synovial Fluid and Serum in Rheumatoid Arthritis and other Rheumatic Diseases.* By JOSEPH J. BUNIM, MORRIS ZIEF, JEROME SIMSON, DENYS K. FORD, and ALFRED SMITH, New York.


*Tendinitis (Bursitis) in the Shoulder.* By AUGUSTUS M. DAVISON, Hot Springs, Ark.

*Treatment of Rheumatoid Arthritis by New Methods of Physical Medicine.* By JOSEPH ECHTMAN New York.

*Long-Term Treatment of Rheumatoid Arthritis with Cortisone.* By EPHRAIM P. ENGLEMAN and MARCUS A. KRUPF, San Francisco, Calif.


*Stellate Ganglion Block for Acute Subdeltoid Bursitis.* By EVERETT J. GORDON, Washington, D.C.


*Pathology of Early Articular Lesions in Rheumatoid Arthritis.* By J. PETER KULKA and DOUGLAS BOCKING, Boston, Mass.


*Effect of ACTH on Acute Disseminated Lupus Erythematosus.* By FREDERIC A. LESTINA, DAVID E. MARKSON, SMITH FREEMAN, and PAUL S. RHoads, Chicago, Ill.


*Effects of Intravenous as compared with Intramuscular ACTH in a Selected Group of Patients.* By BERNARD M. NORCROSS, L. MAXWELL LOCKIE, JOHN H. TALBOTT, and WILLIAM H. GEORGE, Buffalo, N.Y.


*Alterations in Articular Physiology induced by Cortisone and ACTH.* By MARIAN W. ROSES, JANET E. APPLETON, and ELIZABETH L. MANNING, Boston, Mass.

*Rheumatoid Spondylitis with Pregnancy.* By CHARLES L. STEINBERG, Rochester, N.Y.

*Practical Importance of Diurnal Variations in Number of the Circulating Eosinophils.* By J. NORRIE SWANSON, Boston, Mass. (introduced by DR. MARIAN W. ROSES).


* Published in full in the September issue of this Journal (Annals of the Rheumatic Diseases, 1951, 10, 255).