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AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1955

The annual meeting of the American Rheumatism Association was held at Atlantic City, New Jersey, on June 3 and 4, 1955, under the presidency of Dr. Edward W. Boland of Los Angeles. Abstracts of thirty papers and the discussions thereon are printed below. One session was arranged in conjunction with the American Council on Rheumatic Fever and Congenital Heart Disease. Dr. Boland's presidential address formed part of the panel discussion on "New Analogues of Adrenocortical Steroids" (Moderator: Dr. J. J. Bunim). A second panel discussion was held on "Reconstructive Surgery in Arthritis" (Moderator: Dr. Albert J. Key).

Some Aspects of the Chemistry of the Ground Substance of Connective Tissue. By MAXWELL SCHUBERT, *New York, N.Y.* (By invitation.)

Of the three major groups of components of connective tissue, the cells, fibres, and ground substance, the last was considered in connexion with its lubricating, transport, and salt-and-water-binding properties.

The chemical structures of the mucopolysaccharides as at present understood were reviewed, and the properties of solutions of these polysaccharides considered, especially their peculiar behaviour as electrolytes. A clear understanding of the actual distribution and shapes in solution of these long, linear, highly-charged molecules is important in relation to viscosity, ion-binding, water-binding, dye-binding, and the behaviour of ground substance as a membrane. In many connective tissues the mucopolysaccharides are not free but are bound to protein, yet even in such higher complexes they retain their characteristic properties, since their ionic groups are not bound to the proteins to any measurable extent. With proteins that are sufficiently basic, either mucopolysaccharides or mucoproteins can form water-insoluble products. This is thought to be a possible basis for the formation of fibrinoid in rheumatic nodules.

Effects of Leucocytes and Rheumatoid Synovial Membrane on the Viscosity of a Mucoprotein obtained from Cartilage. By MORRIS ZIFF, H. JOEL GRIBETZ, and JOSEPH LOSPALLUTO, *New York, N.Y.*

The effects of cell-free extracts of leucocytes from peripheral blood and of rheumatoid synovial membrane on the properties of a viscous mucoprotein obtained from cartilage were described with reference to the enzymatic alteration of a cartilage constituent by extracts of rheumatoid synovial membrane and local inflammatory cells.

Extracts of human leucocytes and of synovial membrane were prepared by freezing and thawing in distilled water. The substrate was a viscous mucoprotein containing 75 per cent. chondroitin sulphate and 25 per cent. protein, isolated from cartilage. A rapid fall in the viscosity of the mucoprotein was observed, with extracts both of leucocytes and of rheumatoid synovial membrane. The fall in viscosity paralleled that obtained with crystalline trypsin. The amount of fall in viscosity was proportional to the concentration of added extract, and was not changed by adding reducing agents or a variety of proteins. The activity of the extracts showed a maximum *p*H between 5·2 and 6·5; the temperature coefficient of the reaction was 2·5. Heating the extracts rendered them inactive. Soya bean inhibitor blocked the effect of trypsin, but not that of the leucocyte or synovial membrane extracts. Extracts of mouse kidney, lung, liver, and spleen, and of synovial membrane from a patient with osteo-arthritis prepared in a similar manner showed no activity. Solutions of sodium hyaluronate were unaffected.

Sorensen titration has shown that approximately 0·5 per cent. of the nitrogen of the protein residue is split when the viscosity is reduced approximately 50 per cent. Titration of reducing sugar showed no increase in the latter. Recovery of the mucoprotein from solution by precipitation with potassium acetate and alcohol after the viscosity had been reduced demonstrated no change in the nitrogen to hexosamine ratio, but release of chondroitin sulphate from the protein was demonstrated using paper chromatographic technique.

The reduction in viscosity appeared to be due to an enzymatic reaction. The absence of profound change in the composition of the mucoprotein indicated that the fall in viscosity was due to a small but critical change in the composition of the mucoprotein molecule.

If the cartilage mucoprotein may be considered representative of ground substance mucoprotein in general, similar changes may be postulated in association with inflammation in connective tissue disease.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va.*): Has Dr. Gribetz studied normal and rheumatoid arthritic white cells to detect whether there might be any difference between such white cells in this enzymatic activity?

Are we to presume that the white cells themselves in the inflamed synovial membrane contribute to this activity?

DR. GRIBETZ: On a nitrogen basis we have found that the white cells in rheumatoid as well as non-rheumatoid patients showed about equal activity.

We do feel that it is the white cells, or perhaps the lymphoid molecules, which are supposed to be present in the chronic inflammatory tissue of the synovia, and that they contribute towards the activity.

We used a great many of the non-inflamed or non-rheumatoid synovia and found no activity at all.

DR. J. E. WARREN (*Pittsburgh, Pa.*): Why were the extracts from spleen inactive if the lymphocytes were the active principle?

DR. GRIBETZ: We repeated the experiment with a variety of animals—guinea-pig, rabbit, rat—and always found the spleen inactive. Some more recent work seems to indicate that there may be something inhibitory in splenic extracts, but this work is too recent to elaborate upon. We tried a variety of extraction procedures, but had no activity with splenic extracts.

Experimental Studies on Protracted Hypersensitivity of the Serum Sickness Type. By FREDERICK G. GERMUTH, JR., *Baltimore, Md.*

Histological and quantitative immunological studies were undertaken with the use of homogenous foreign proteins to determine:

(*a*) the relationship between immune response and the evolution of allergic lesions;

(*b*) the effects of antigen dosage, type of antigen, and chronicity of antigen administration on the development of allergy.

The results of these studies bear on the pathogenesis of human polyarteritis nodosa and there is experimental evidence for the role of hypersensitivity in other so-called collagen diseases and glomerulonephritis.

Histological and Clinical Evolution of Lupus Nephritis.* By ROBERT C. MUEHRCKE, ROBERT M. KARK, CONRAD L. PIRANI, VICTOR E. POLLAK, and IRVING E. STECK, *Chicago, Ill.*

The microscopic changes in kidneys of 32 patients with lupus erythematosus disseminatus (L.E.D.) was studied by serial renal biopsies. Histological data were correlated with changing clinical status, clinical laboratory data, and gross and discrete renal function tests in a continuing study of the histological evolution of the kidney involvement.

Renal lesions progressed from normal to early involvement of the glomeruli—local glomerulitis—which was characterized by "fibrinoid condensation", and local cellularity. In the course of lupus nephritis, the lesion progressed to patchy glomerulitis, general glomerulitis, and thickening of the basement membrane, to form "wire loops", and to typical subacute glomerulonephritis with epithelial crescents.

Two distinct groups of patients with nephrotic oedema were observed. One group had the nephrotic syndrome (criteria of Leiter) and microscopic findings of subacute glomerulonephritis. The second group had a pseudonephrotic syndrome with low or normal serum cholesterol and cholinesterase levels. Histological study of the renal biopsy from the second group revealed severe glomerular changes with severe capillary hyalinization and digitation of glomeruli. In these patients the disease was rapidly fatal.

Urine findings and kidney histology were correlated: white blood cells and white blood cell casts were found during the stage of local glomerulitis. Persistent proteinuria was usually found with general glomerulitis. Marked impairment of renal function was observed in the "wire-loop" and glomerulonephritic stage of lupus nephritis. A fixed urine specific gravity and, in a few cases, hypertension accompanied the chronic glomerulonephritis.

Discussion.—DR. PETER FORSHAM (*San Francisco, Calif.*): In this pseudo-type, with the low cholesterol level, have you any liver function tests that would indicate that those patients have marked liver damage and that that is why the cholesterol is low?

DR. MUEHRCKE: Various tests of liver function were done on patients with the pseudonephrotic syndrome due to lupus nephritis. The cephalin flocculation, serum bilirubin levels, prothrombin time, and bromsulphophthalein retention were normal. As observed in other patients with severe lupus erythematosus the thymol turbidity was elevated, but the serum cholinesterase level was depressed below normal.

DR. THEODORE B. BAYLES (*Boston, Mass.*): Was there evidence of amyloid in these kidney biopsies?

DR. MUEHRCKE: Sections of the kidney biopsy from patients with lupus nephritis were stained with Congo red and crystal violet. There was no histological evidence of amyloid.

DR. MORRIS ZIFF (*New York City*): Could Dr. Muehrcke elaborate a little more on the effect of cortisone therapy on the course of these lesions?

DR. MUEHRCKE: Large doses of cortisone and other steroid hormones have been reported to produce glomerular lesions of rat and rabbit kidneys. Although there is much speculation on the effect of steroids on the human kidney, no definitive work has been done.

We have studied the renal function and kidney histology of patients with rheumatoid arthritis, including some who had been on prolonged cortisone therapy and have seen no renal lesions that could be attributed to steroid or ACTH therapy.

DR. MORRIS ZIFF: With these patients receiving cortisone, was the progress of this lesion influenced?

DR. MUEHRCKE: Our studies indicate that cortisone does not seem to influence the renal lesion in lupus erythematosus. Urinary findings of proteinuria, cylindruria, and azotaemia of the acute stage may disappear on cortisone therapy as the clinical course of the patient improves. These findings are probably associated with fever and dehydration rather than with lupus nephritis.

Musculoskeletal Manifestations of Disseminated Lupus Erythematosus, Polyarteritis Nodosa, Dermatomyositis, and Diffuse Scleroderma. By W. M. MIKKELSEN, H. A. ZEVELY, N. H. CHATELIN, and I. F. DUFF, *Ann Arbor, Mich.*

From the University of Michigan Hospital necropsy series fifty cases of "connective tissue disease" were reviewed. Musculoskeletal manifestations were prominent in eighteen of 21 cases of disseminated lupus erythematosus, fourteen of eighteen cases of polyarteritis nodosa, and all of five cases of dermatomyositis and six cases of diffuse scleroderma. At some time during the illness the diagnosis of rheumatoid arthritis or rheumatic fever was erroneously applied in eleven cases of disseminated lupus erythematosus, four cases of polyarteritis nodosa, three cases of dermatomyositis, and four cases of scleroderma.

Careful review of the clinical and pathological features

* This paper is given in full on p. 371 of this issue (*Annals* (1955), 14, 371).

of these cases revealed characteristic differences on the basis of which accurate clinical diagnosis was usually possible. Objective joint findings were not of differential value, but joint contracture without intra-articular disease occurred only in dermatomyositis and scleroderma. Disseminated lupus erythematosus differed from rheumatoid arthritis in the more frequent occurrence of erythematous facial eruptions, leucopenia, and renal, cardiac, and serous membrane involvement. Peripheral neuritis and gastro-intestinal symptoms were of greatest value in recognizing polyarteritis nodosa; other valuable findings included bronchial asthma with eosinophilia exceeding 25 per cent., hypersensitive renal disease, persistent unexplained fever or leucocytosis, nodular or necrotic skin lesions, intermittent testicular pain, and *x*-ray picture of "diffuse granular disease" of lung. The muscular involvement in dermatomyositis and the skin changes in scleroderma were readily distinguished from similar but milder findings in the other diseases.

The possibility of one of these diseases, and especially of disseminated lupus erythematosus, should be considered in cases of rheumatoid arthritis that are "atypical' or associated with multiple system involvement.

Discussion.—DR. GERALD P. RODNAN (*Bethesda, Md.*): Our experience and that of others would appear to differ from that of the speaker regarding joint involvement in scleroderma. We have had the opportunity to obtain synovial biopsies from the supra-patellar bursa of a number of patients with diffuse scleroderma. Four of these had symptoms and signs of frank arthritic involvement of the hands, knees, and other joints.

In patients with symptoms and signs of arthritis, the biopsy revealed acute or chronic synovitis, with focal areas of fibrosis besides other pathological changes.

Lupus Erythematosus Cell Reaction: Its Morphology and Specificity. By M. A. OGRYZLO, *Toronto, Ont.*

The L.E. cell reaction, as commonly performed, is an *in vitro* phenomenon which may be observed in patients with acute disseminated lupus erythematosus, when plasma, serum, or serous effusions are permitted to stand for a period of time in contact with a mixture of freshly-drawn white-cell elements of the blood or bone marrow. This test has been performed on more than 880 occasions in a large variety of patients to study the morphology of the typical L.E. cell and so-called rosette, and determine the specificity of the reaction for lupus erythematosus. Coloured photographs showed clearly the sequence of events in the development of the L.E. cell and rosette, the source of the inclusion material, and the various forms which may be encountered. While the characteristic L.E. cell is a mature neutrophil, evidence has been obtained that virtually all leucocytes are capable of taking part in both the degenerative and phagocytic phases of the reaction. These include eosinophils, basophils, monocytes, lymphocytes, and even plasma cells. Although the test was positive in 28 patients with acute disseminated lupus erythematosus, it was negative in three such patients, and occasional positive reactions were observed in patients with other diseases, including nine with classical rheumatoid arthritis, and one each with scleroderma, polyarteritis nodosa, dermatomyositis, Hodgkin's disease, and haemolytic anaemia. Two patients showed a positive test during a reaction to phenylbutazone therapy and one patient after a reaction to hydralazine therapy. These observations suggest that the phenomenon may represent a particular hypersensitive state, but that it cannot be regarded as entirely specific for lupus erythematosus and may be reversible when the sensitizing agent is withdrawn.

Discussion.—DR. C. L. STEINBERG (*Rochester, N.Y.*): In the rheumatoid arthritis patients with positive L.E. cells in marrow, were many L.E. cells found in these smears, or on many occasions? My own experience is that when L.E. cells are found in rheumatoid arthritis they are much fewer in number and much more difficult to find on subsequent occasions.

DR. OGRYZLO: All the rheumatoid arthritis patients referred to in this paper who had positive tests showed L.E. cells in from 2 to 15 per cent. of the nucleated cell count, which would have to be regarded as fairly large numbers. The proportion was relatively constant in each patient on repeated tests.

DR. LAWRENCE E. SHULMAN (*Baltimore, N.Y.*): We also have had several cases of false positive reactions, for example, in scleroderma which at times is associated with lupus. Patients with lupus sometimes present with a picture of Hodgkin's disease, but subsequently show widespread evidence of lupus; occasionally acute haemolytic anaemia is the initial manifestation and widespread lupus is found if the patient is followed long enough.

I do not mean to say there are no false positive reactions, but that we should be cautious in these cases.

DR. OGRYZLO: I agree with Dr. Shulman that many patients with lupus erythematosus may initially present with symptoms resembling other diseases. However, some of the patients referred to in the paper with positive tests were examined at *post mortem* and lacked the findings associated with lupus erythematosus, including the patient with Hodgkin's disease and some of those with severe, long-standing rheumatoid arthritis. In the two patients who suffered a reaction to butazolidin, the test has become negative with recovery. On a clinical basis it would be difficult to accept these patients as suffering from lupus erythematosus. I might add that I do not regard these as false positive tests, but rather as positive tests due to the presence of other diseases. There is some indication that it represents a type of immune response which is not necessarily specific for lupus erythematosus, although most characteristic for that disease. In some instances the reaction may be reversible and disappear.

DR. JOHN H. VAUGHAN (*Richmond, Va.*): I should like to ask about the lymphocyte which has apparently engulfed some nuclear material. I believe it is the experience of most people that the lymphocyte, at least under ordinary conditions, is not a phagocytic cell. Therefore, I should like to ask whether you are sure it was a lymphocyte; and how often you have seen this? If they were, indeed, lymphocytes, it represents an extraordinary stimulus to phagocytosis.

DR. OGRYZLO: We have seen a wide variety of phagocytic cells ingesting the nuclear bodies. There is no doubt about lymphocytes being phagocytic. I could show many examples of lymphocytes and also eosinophils behaving in a phagocytic manner and taking up the altered nuclear material. They have been observed both in fixed smears and in the living motile state.

A Study of Disseminated Lupus Erythematosus diagnosed in Patients formerly considered to have Rheumatoid Arthritis. By FRANCIS W. MCCOY, MARJORIE PATTERSON, and R. H. FREYBERG, *New York, N.Y.*

As knowledge about lupus erythematosus has increased and diagnostic aids have been improved, many patients considered to have rheumatoid arthritis with complications or an atypical form of this disease were studied to determine whether they had disseminated lupus erythematosus. Typical L.E. cells were found in the blood of approximately 25 per cent. of eighty patients in this group. These patients whose diagnosis of disseminated lupus erythematosus was *based upon the L.E. cell test* were carefully re-evaluated in regard to the behaviour of the rheumatic disease and the clinical and laboratory characteristics of the non-rheumatic illnesses.

The question whether the disease currently considered to be rheumatoid arthritis is changed into a different illness by means of therapeutic agents, was discussed.

If all patients who have L.E. cells in their blood have lupus erythematosus, the following should be emphasized:

(1) Disseminated lupus erythematosus is much more common than previously considered.
(2) Disseminated lupus erythematosus usually is more often a chronic illness; in only a small per cent. of patients is it acute, severe, and fatal.
(3) The rheumatic component of disseminated lupus erythematosus may be indistinguishable from rheumatoid arthritis.
(4) Treatment for each illness is similar in many aspects.
(5) Prognosis of disseminated lupus erythematosus is better than it was formerly considered to be.

Discussion.—DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): We searched for lupus cells in the blood of 1,600 consecutive admissions to our arthritis clinics, using the 2-hour clot method; 520 were diagnosed as having rheumatoid arthritis, and in sixteen (3 per cent.) of them, positive identification of the L.E. cell was made; 129 of the rheumatoid group were classed as atypical rheumatoid arthritis, and of these only one exhibited L.E. cells.

182 of the 520 rheumatoid patients were receiving cortisone at the time of admission to the clinic; thirteen of these cortisone-treated patients produced L.E. cells, as against three who had received no cortisone.

DR. CHARLES H. SLOCUMB (*Rochester, Minn.*): We carried on a similar series of studies and came to much the same conclusions as Dr. McCoy, but I feel that in rheumatoid arthritis and lupus erythematosus the prognosis is different, and that there are sufficient differences in treatment to require the clinician to be extremely careful to differentiate between the two diseases.

In a group of 67 patients with acute lupus, 93 per cent. had positive L.E. tests. In a group of 105 rheumatoids who had not had steroids, 5 per cent. had a positive L.E. test. In a group of 27 patients in whom the rheumatism was not diagnostic, 78 per cent. had lupus and were probably lupus cases.

Granted that some patients cannot be distinguished over a period of weeks or even months by their rheumatism alone and that we have to go by their systemic reaction, it remains to be seen whether the 5 per cent. of patients with the positive lupus reactions are going to react differently from the other rheumatoids, and whether they will turn out to be rheumatoids or lupus patients.

Statistically, there is no set test which will distinguish between the two diseases; in favour of rheumatoid arthritis is the persistence of synovitis, joint destruction, leucocytosis, and lowered globulin, but any of those can be duplicated in lupus erythematosus.

In favour of lupus is a recurrence of the synovitis with clearing, high fever, cerebral manifestations, leucopenia and lymphocytosis, thrombocytopenia, false flocculations, and, of course, the positive L.E. test.

One other difference in our analysis is that rheumatoid patients who had been given large doses of cortisone showed a significant difference in the occurrence of positive L.E. reactions (to be reported in a later paper by Dr. Palmer). In those who had had small amounts of cortisone, the percentage remained the same: 5 per cent. had a positive L.E. cell reaction.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Has any attempt been made to correlate the past history of gold therapy with these degenerative phenomena in the leucocytes? The three cases illustrated had all had gold; perhaps this rather than the cortisone, might have been a factor.

DR. MCCOY: It is very difficult to attempt to classify these patients, but we have several who exhibit a positive L.E. phenomenon, who are taking nothing but aspirin, and are relatively asymptomatic, and one of these also received one short series of meticorten.

Many patients come to our clinic from elsewhere, and it is very difficult to obtain all the facts from them.

DR. WALLACE GRAHAM (*Toronto, Ont.*): How many of the 520 rheumatoid patients had had gold therapy?

DR. W. K. ISHMAEL (*Oklahoma City*): Less than 150.

DR. CHARLES RAGAN (*New York, N.Y.*): Can Dr. McCoy tell me the number that had a positive test at 2 hours and the number that had a positive test at 24 hours? I think a positive test in 24 hours is unusual.

DR. MCCOY: Most of the patients were positive at the end of a 2-hour period. We reviewed the 24-hour and 12-hour smears incubated at room temperature to see whether the time element increased positivity.

DR. ANDRIES I. RODENBERG (*Rochester, N.Y.*): Are there any *post-mortem* studies on patients with atypical or typical rheumatoid arthritis with positive L.E. cells?

DR. MCCOY: The only patient in the series in which we are interested who died did not die at our hospital, but at another hospital in New York City, where the pathology report sent to us was compatible with a diagnosis of disseminated lupus erythematosus. That is the only *post-mortem* study I know of.

DR. M. A. OGRYZLO (*Toronto, Ont.*): Regarding the question of gold, we have not observed any positive tests even in those with severe reactions and renal damage. At the present time we are following three such patients, one of whom showed a doubtful test but was recorded as negative because the cells were entirely typical. I feel that gold, like other sensitizing agents, may be capable of inducing a positive test, but we have not encountered one.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): A very practical and important question is whether or not the presence of an L.E. phenomenon in a patient who is considered to have rheumatoid arthritis contra-indicates the administration of gold. Such a question does not pertain to cortisone, because if we assume the patient has lupus erythematosus, cortisone is certainly indicated; but we should be clear whether gold will precipitate or intensify the systemic manifestations.

DR. MCCOY: I can only say that some of our patients who have a positive L.E. cell phenomenon have been receiving gold and are taking it now. We hope by reviewing them to find out whether they were more sensitive as a group, but the statistics are not yet available.

DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): All our patients who appear to have rheumatoid arthritis with a positive L.E. cell reaction are still alive, but 50 per cent. of those with the classical stigmata of disseminated lupus erythematosus have died during the observation period of 2 years. The latter are not included in our figures as they were seen at another hospital.

Recognition and Treatment of Patients with Chronic Hypercortisonism. By HOWARD F. POLLEY, CHARLES H. SLOCUMB, L. EMMERSON WARD, and PHILIP S. HENCH, *Rochester, Minn.*

Patients who develop chronic hypercortisonism during the treatment of rheumatoid arthritis produce a syndrome of alternating periods of mental stimulation, restlessness, and lack of interest in responsibilities, alternating with periods of emotional instability, fatigability, weakness, and aching in the muscles and joints.

A pan-mesenchymal reaction occurs in many of these patients during periods of withdrawal of the hormone. The reaction may simulate flares of L.E., periarteritis, or rheumatoid arthritis. The diagnosis, treatment, and prognosis of a large group of these patients is reviewed.

Discussion.—DR. PETER FORSHAM (*San Francisco, Calif.*): This very excellent and provocative presentation calls for a few comments, for it leads one to question the rationale of maintenance corticoid therapy.

We were shown that if one has a patient on very high doses of corticoids and is then suddenly forced to reduce this dosage because of side-effects, one finds oneself in a dilemma, because the disease flares up and sometimes in a more malignant fashion than before.

We are told that this can be prevented simply by staying below the tolerable dosage. Actual daily dosages coincide closely with the estimate of the daily output of hydrocortisone by the normal human adrenal not subjected to stress, which happens to lie between 30 and 40 mg. hydrocortisone per day. If, then, we follow the safe procedure of staying below the toxic levels—toxic to some patients and not to others—we merely suppress pituitary ACTH production by amounts of hydrocortisone equivalent to the normal adrenal cortical output. What have we done by replacing the output of the adrenal cortex in man by 40 mg. of a known steroid? Why should the patient get better?

Two possibilities arise. Do we suppress some hormone from the adrenal cortex which is bad as far as the disease is concerned, and replace that by something which is essentially good for rheumatoid arthritis? Evidence for this is not readily available, but one has to keep this possibility in mind. Alternatively, although you merely suppress and replace, perhaps the exogenous hormone administered every 6 hours is more constant than the variable levels built up by the normal human adrenal cortex. This afternoon Dr. Vincent Di Raimondo is to report on the activity of the human adrenal cortex in normal subjects; it is very active in the early morning hours, very inactive in the late afternoon, and practically asleep around midnight. This may be related to the fact that the arthritic patient feels comparatively well during the day and stiffens up in the late afternoon and evening.

The maximum adrenal cortical secretion during a 24-hour period is ten times greater than the lowest point, and if you substitute for this variable level a dose of the same hormone round the clock in equal amounts every 6 hours you may be doing better for the patient.

Although the maintenance doses of hydrocortisone and related corticoids appear very small and may be expected, on logical grounds, to do little more than normal adrenals, they may possibly prove helpful by providing the type of steroid which prevents inflammatory reaction while suppressing the endogenous steroids which increase it, and by assuring a constant level in the blood, in contrast to the tidal action of the human adrenal cortices.

DR. POLLEY: Dr. Forsham has commented on a number of aspects of the problem of exogenous hypercortisonism which could not be included in the time for our presentation. He has answered his own remarks concerning the value of cortisone therapy. Our discussion is directed toward the effects of chronic *overdosage* and cannot be interpreted as indicative of the value of hormonal therapy with optimal dosage. Hormonal therapy is no more indicated for all patients with rheumatoid arthritis than insulin for all patients with diabetes mellitus or surgery for all patients with duodenal ulcer. In the factor of dosage, cortisone and related hormones may be compared to many other therapeutic substances. Complications of overdosage from digitalis, aspirin, insulin, or sedatives, for example, do not negate the value of these drugs when used in appropriate amounts. Similarly, the problems of overdosage with cortisone, corticotropin, or related hormones should not negate the therapeutic value of optimal doses of these hormones.

DR. WALTER BAUER (*Boston, Mass.*): I find it difficult to believe that all the symptoms that Dr. Polley has ascribed to chronic hypercortisonism in his patients with rheumatoid arthritis are really manifestations of hypercortisonism. He has not convinced me that the hypercortisonism causes increased inflammatory changes of the affected mesenchymal tissue. Furthermore, some of the cases that he has reported may have lupus erythematosus disseminatus and not rheumatoid arthritis. If the many changes in the mesenchymal tissue that he ascribes to hypercortisonism do occur, why are they not seen in patients with long-standing Cushing's disease?

DR. J. ALBERT KEY (*St. Louis, Mo.*): Since they have lowered their maintenance dose, what do they do about the beginning of the treatment, and how much do they give before running into danger?

Secondly, has ACTH a place in the treatment of hypercortisonism? It would seem logical to give smaller doses of ACTH to try to stimulate the adrenal cortex as you decrease your substitution hormone.

DR. POLLEY: I will respond first to Dr. Bauer's comments. We, too, have recognized that certain of the significant features of chronic hormonal overdosage in patients with rheumatoid arthritis have not been recognized in patients with endogenously-induced Cushing's syndrome. A satisfactory explanation for this difference undoubtedly awaits further study of both diseases, but it appears that the mesenchymal responses to chronic hormonal overdosage in the patient with rheumatoid arthritis differ from the reactions due to exogenous or endogenous hormonal excesses in a patient without rheumatoid arthritis.

The question whether the rheumatoid patient in whom a diffuse mesenchymal reaction simulating lupus erythematosus develops from chronic hormonal overdosage is

in reality a patient with lupus erythematosus is, of course, an important one. In our experience the rheumatoid patient with a mesenchymal reaction resulting from hormonal overdosage has generally reverted to the previous rheumatoid pattern of tissue response if the excess of hormonal dosage is satisfactorily corrected while the mesenchymal reaction is still in a reversible stage. In our studies the incidence of mesenchymal reactions among rheumatoid patients with hypercortisonism was significantly greater than among a comparable group of rheumatoid patients who had not had hormonal therapy.

In answer to Dr. Key's question, we estimate an initial hormonal dose for rheumatoid arthritis by considering first the patient's sex and age. We prefer to keep initial doses within the anticipated limits of tolerance for the maintenance doses. This avoids the stimulating effects of large doses and makes prolonged hormonal therapy more satisfactory. The slower antirheumatic response to small doses is more acceptable to us than the difficulties resulting from prolonged use of doses in excess of the anticipated tolerance. In our experience the highest maintenance dose of cortisone tolerated by postmenopausal women is approximately 25 to 30 mg. a day, by premenopausal women 35 to 40 mg. a day, and by adult men 40 to 50 mg. a day. Generally these are upper limits; we like to keep below these maximal doses, whether it is the first or hundredth day of treatment.

Use of corticotropin "to stimulate the adrenal cortex" of a patient with chronic hypercortisonism while the excessive dose of cortisone is being decreased may apparently improve symptoms of the mesenchymal reaction, but this is only a temporary effect when it occurs. The addition of corticotropin may thus perpetuate rather than correct the state of hypercortisonism. Very gradual decreases of hormonal dosage with discontinuation of hormonal therapy if necessary has so far been the most reliable long-term approach to the correction of chronic hormonal overdosage.

Treatment of Systemic Lupus Erythematosus with Prednisone and Prednisolone. By ALFRED JAY BOLLET, STANTON SEGAL, and JOSEPH J. BUNIM, *Bethesda, Md.*

Ten patients with systemic lupus erythematosus, in whom the disease was not satisfactorily controlled by cortisone, hydrocortisone, corticotropin, or combinations of these hormones, were given prednisone (metacortandracin) or prednisolone (metacortandralone) after a suitable period of control observation. The initial suppressive dose varied between 20 and 60 mg. per day, and the minimum maintenance dose between 5 and 30 mg. per day. These drugs were found to be approximately four times more potent than the other steroids, and no difference was noted between prednisone and prednisolone. The synthetic steroids were very effective in suppressing the systemic manifestations of lupus, such as chills, fever, and malaise; skin and mucous membrane lesions healed, and leucopenia improved. The anaemia was not usually altered, and the L.E. phenomenon persisted. The C-reactive protein when present disappeared on therapy, and the sedimentation rate decreased, but did not usually become normal. Pulmonary and pleural changes were rapidly reversed, although patches of rales occasionally persisted. Cardiac murmurs and pericardial friction rubs improved, but enlargement of the heart and E.C.G. abnormalities did not. Azotaemia and urinary abnormalities receded only when they had previously been aggravated by systemic toxicity or other extrarenal factors. In patients with nephrotic syndrome, no alteration in protein excretion occurred. No improvement in electrolyte abnormalities (*e.g.*, hyponatraemia and hyperkalaemia) occurred on treatment, and no alterations in blood pressure were noted either in the three hypertensive patients, or in those with normal tension. Retinopathy cleared in one of three instances. Serum albumin levels increased slightly on treatment in most patients, but did not return to normal in any; elevated serum globulin levels, which were present in six patients, decreased slightly in some but did not return to normal. Oedema, which was present in three patients, diminished in all, but disappeared completely in only one. Convulsions and mental changes apparently due to "lupus" lesions in the central nervous system were improved, but E.E.G. abnormalities were not altered. In general, these patients were somewhat better on maintenance doses of prednisone than on previous steroids, and no serious side-effects were noted.

Discussion.—DR. CHARLES LEROY STEINBERG (*Rochester, N.Y.*): Lupus erythematosus is a disease with many systemic manifestations, and the evaluation of the effect of any drug on the clinical course of such a complex disease becomes difficult.

In general, our conclusions are the same as those given by Dr. Bollet and his group. We have had the opportunity of treating seven patients with systemic lupus and three patients with periarteritis nodosa with prednisone. The effect on the cholesterol in some of these patients was interesting and complex. Renal manifestations are frequent in systemic lupus, and in some of our patients the cholesterols and cholesterol esters rose while they were under metacortandracin therapy.

The question arose whether we had aggravated a renal lesion such as have been stated to occur when cortisone and corticotropin were first tried in this disease, but we found that neither the azotaemic level nor the urinary findings followed the cholesterol level.

One patient with periarteritis nodosa died while under treatment. The autopsy showed most extensive arterial involvement, both visceral and peripheral, and a remarkable feature was that the histological studies showed no inflammatory process in the diseased arteries, the inference being that, if this patient had been treated earlier, the outcome would have been favourable. Two other patients with periarteritis nodosa have been converted from very sick to employable.

The seven patients with L.E. had previously been treated with either cortisone or corticotropin, and all have done very well with prednisone, but in no instance did the L.E. cells disappear from the bone marrow or the peripheral blood. In one instance in which the white blood count was as low as 1,300 on 150 mg. cortisone daily, it rose to normal on prednisone and has remained so for several months.

All seven patients carry on their usual activities with little or no restriction, and can tolerate a normal diet with no salt restriction or doses of potassium.

The initial dose used was 30 mg. per day, and except the individual who died with periarteritis nodosa, these patients have had nearly 4 months' observation. The

dose was decreased by 5 mg. every 5 days until the least amount required for maintenance was reached, usually in the region of 15 to 20 mg. per day. We have not been able to reduce our dosage to as low as 5 mg.

DR. GERALD P. RODNAN (*Bethesda, Md.*): We have used prednisone in six patients with progressive systemic sclerosis. There were four women and two men in this series, and the duration of the illness ranged from $1\frac{1}{2}$ to $6\frac{1}{2}$ years. In addition to widespread cutaneous disease, they all presented involvement of at least one other system. Subcutaneous calcinosis was clinically and/or roentgenographically demonstrable in three. In three there was frank polyarthritis, particularly in the hands and knees, the sheep cell agglutinin titres were 4, 16, and 32. Clinical and/or radiological evidence of oesophageal involvement was present in five. In one woman there were symptoms referable to small bowel disease, and *x* rays demonstrated marked abnormalities in gut motility and mucosal pattern. One 60-year-old male, much troubled with exertional dyspnoea, was found to have an enlarged heart, reticular pulmonary fibrosis, and an abnormal electrocardiogram.

Skin biopsy in each instance confirmed the impression of scleroderma. In those patients with arthritis, synovial biopsy revealed acute or chronic synovitis, characterized by infiltrates of lymphocytes and plasma cells, with focal fibrosis.

A base-line observation period of approximately one month was obtained, when serial review of symptoms and physical findings was made. Following a course of placebo medication, the patients received prednisone, 30 mg. per day in divided doses orally. While on medication, the patients had 3 g. sodium per day.

The most dramatic response to this treatment was observed in those patients with joint involvement. Within 48 hours they noted marked alleviation of pain and stiffness. This improvement continued and has persisted for up to 4 months on therapy. Changes in the skin were evident usually within a week, with diminution in the tightness, oedema, and hyperpigmentation. Skin previously stretched taut could be wrinkled. Only slight change was noted in those areas in which the skin had undergone marked atrophy.

The patient with cardio-pulmonary disease experienced considerable improvement in his dyspnoea and pulmonary function studies demonstrated a marked increase in maximal breathing capacity. The electrocardiogram and chest film remained unchanged. The woman with small bowel difficulty continued to have considerable distress, with gaseous distention and motility disturbances.

There was an increase in haematocrit and a fall in erythrocyte sedimentation rate and C-reactive protein. The eosinophil counts were reduced sharply. With few exceptions, changes in the serum protein level were slight and of questionable significance.

No changes were apparent in *x* rays of the joints and gastro-intestinal tract or in the appearance of skin and synovial biopsies obtained after a month or more.

Side-effects were minimal, apart from the occasional development of mild facial rounding and acne. Blood pressure remained normal and there was no fluid retention.

Observations on Prolonged Administration of Metacortandracin in Rheumatoid Arthritis. By ROGER L. BLACK, ALFRED J. BOLLET, STANTON SEGAL, and JOSEPH J. BUNIM, *Bethesda, Md.*

Eighteen patients with active, progressive rheumatoid arthritis who had failed to respond satisfactorily to aspirin, gold compounds, cortisone, hydrocortisone, corticotropin or phenylbutazone, and who exhibited in most instances striking improvement when given metacortandralone or metacortandracin, received the new steroid for periods varying from 6 to 10 months.

The adrenal cortical function was suppressed and undesirable side-effects occurred, including facial rounding, diminished carbohydrate tolerance, duodenal ulcer formation, and mental disturbance. In some patients the maintenance dose had to be increased to sustain the improvement initially achieved.

The early impression has been confirmed that the new steroids are four times more potent than cortisone or hydrocortisone and that when reversible changes are present maximal rather than "suboptimal" improvement can usually be attained without increased hazard.

Discussion.—DR. C. PLOTZ (*New York City*): We owe Dr. Bunim and his group a debt for their pioneer work with this new hormone.

We all have to share the blame for the interval between the favourable report and the reports of toxic reactions; six weeks ago in a report on over 1,000 patients, the incidence of side-reactions was only about 11 per cent., and this is clearly due to a lag in reporting these side-reactions to the manufacturers.

We have used this hormone in 42 patients; two developed peptic ulcers and one acute thrombophlebitis, in one an old fibrotic pulmonary lesion became active, one became severely depressed and made an unsuccessful attempt at suicide, and one with psoriasis and rheumatoid arthritis who had previously been controlled successfully on ACTH and on cortisone had a severe exacerbation of her psoriasis though the arthritis was controlled.

The last patient in whom we had to discontinue treatment with metacortandracin was quite unusual. She had an undiagnosed mesenchymal disease, possibly lupus, about 50 per cent. diminution in renal function. She was put on prednisone in doses of 20 to 30 mg. daily for 4 weeks, but the hormone had to be discontinued because she had gained 11 lb. of oedema fluid.

DR. WILLIAM H. KAMMERER (*New York City*): Our experience with Meticorten (metacortandracin) dates from Nov., 1954, since when we have observed its effects in 96 patients; 76 had rheumatoid arthritis; and 44 have now been under observation for 3 to 6 months. A great many have now been put into Grade I and II and Classes I and II; this appears impressive, but does not tell the whole story, for many of them had been on intra-articular hydrocortisone at varying intervals; some had had Butazolidin as an analgesic agent, and all were receiving a substantial amount of salicylates. Since prednisone therapy was begun, many of these added measures have been discontinued.

Out of 41 patients on long-term steroid therapy, many went from Grade III and IV on cortisone and hydrocortisone to Grade I and II on prednisone, and I think we must agree that prednisone is a better antirheumatic agent than cortisone and hydrocortisone, but we do not know what the long-term effect of prednisone in the treatment of rheumatoid arthritis will be, and we probably shall not have the answer for 2 or 3 years. In the past 2 or 3 weeks, several patients who had been on prednisone therapy for 4 to 6 months have begun to have a flare in activity while continuing with the dosage which had previously controlled their symptoms. It may be that long-continued therapy will result in the "petering

out", as Dr. Cecil describes it, of the antirheumatic effect, but only time will tell.

With regard to calcium metabolism and the possible occurrence of peptic ulceration, in our group of 96 patients we discontinued prednisone in three: in one because of radiologically proven gastric ulcer, in one because of symptomatology of peptic ulcer, and in one because of phlebitis. These side-effects do occur, but we should not magnify them out of proportion. I agree with Dr. Plotz that mooning and other minor side-effects may be somewhat more prominent, but though they are undesirable there is no solution for them. The patient must accept either the minor side-effect or the rheumatoid arthritis.

Comparison of the Metabolic Effects of Prednisone and Cortisone. By EVAN CALKINS, LEON REZNICK, and WALTER BAUER, *Boston, Mass.*

In order to study the many variables influencing calcium, nitrogen, and phosphorus metabolism in rheumatoid arthritis, a patient was selected with disabling dermatitis, confined to the finger tips and not accompanied by systemic manifestations, and 12-day periods of therapy with prednisone (Meticorten) and prednisolone (Meticortelone) in oral doses of 75 mg. daily, were compared with a 12-day period of treatment with 300 mg. cortisone daily. Control periods of 12 or 16 days intervened between treatments. Both prednisone and prednisolone caused losses of nitrogen (4 g./24 hr) and phosphorus (0·3 g./24 hr). Cortisone caused much smaller losses (0·5 g. nitrogen and 0·05 g. phosphorus). Both prednisone and cortisone caused an increase in urinary calcium excretion (0·03 g./24 hr).

Five patients with pemphigus vulgaris were treated with prednisone, 80-120 mg. per day. All displayed alterations in carbohydrate metabolism as great as or greater than previously observed with cortisone or ACTH. This consisted in one or more of the following: marked abnormalities in glucose tolerance, elevation in blood sugar (as high as 300 mg. daily), glycosuria (as high as 100 g./24 hr), and marked elevation in plasma lactate and serum pyruvate both while fasting and during the glucose tolerance test.

This data, in agreement with recent evidence from other clinics, indicates that, in comparison with cortisone, prednisone exhibits, milligram for milligram, greatly enhanced metabolic as well as antirheumatic effects.

Discussion.—DR. CARL STEVENSON (*New York City*): Hyperglycaemic effects of cortisone acetate, hydrocortisone acetate, and prednisone were studied in a 53-year-old female patient with rheumatoid arthritis. The unexpected finding of glycosuria during a previous short course of cortisone prompted the investigation.

A moderate disturbance of carbohydrate metabolism was present when the cortisone was administered, manifested by a fasting blood sugar of 168 mg./100 ml. This was later shown to be a residual effect of the previous, short period of cortisone administration which ended 18 days before this study began. The initial dose of cortisone was 200 mg. daily, with later doses of 150 and then 100 mg. daily (Figure, overleaf).

Large doses of cortisone were continued despite evidence of severe disturbance of glucose metabolism, since ketosis, acidosis, and weight loss did not occur, and because the patient continued to feel well. The hormone was discontinued after 75 days of administration, and after 115 days of no medication the glucose tolerance had reverted almost to normal. (The fasting blood sugar was normal; the peak value of blood sugar during a glucose tolerance was 192 mg./100 ml.)

Hydrocortisone acetate was then injected intramuscularly in doses of 100 mg. daily. The glucose tolerance was noted to change significantly on the 15th day; the fasting blood sugar became elevated between the 25th and 35th days. Again, no other adverse effects were noted. After the cortico-steroid was discontinued there was gradual improvement of carbohydrate metabolism; the glucose tolerance was normal 180 days later.

Three years later this patient participated in a similar study of prednisone. Several pre-treatment glucose tolerance tests revealed a persistent, mild asymptomatic diabetic state. Fasting blood sugar values ranged from 100 to 120 mg./100 ml. with peak tolerance values up to 220 mg./110 ml.

The initial dose of prednisone was 40 mg. daily. Between the 15th and 35th day a steroid-induced diabetic effect similar to that with cortisone and hydrocortisone was noted. After the drug was discontinued this state began to improve, and the pre-prednisone status was attained in about 120 days.

This patient developed a temporary severe carbohydrate metabolic disturbance when treated with cortisone acetate, hydrocortisone acetate, and prednisone. These results indicate similar "diabeticogenic" effects from all three of these cortico-steroids.

* * * *

PANEL DISCUSSION

(MODERATOR: DR. J. J. BUNIM)

Newer Analogues of Adrenocortical Steroids

(see Table, overleaf)

Biosynthesis and Metabolism of Adrenocortical Hormones. By RALPH I. DORFMAN, *Shrewsbury, Mass.*

The adrenal cortex produces a variety of steroid hormones under the influence of adrenocorticotropic hormone (ACTH). The action of ACTH seems to be threefold:

(A) the growth of all the cortical elements, which probably occurs in a matter of days;
(B) the formation of specific biosynthetic enzymes, which probably occurs in hours;
(C) a direct action on the biosynthetic mechanisms which occurs in minutes.

On the basis of the best evidence, biosynthetic reactions in the adrenal may be considered to start from acetate and cholesterol and proceed by two independent reaction sequences to the corticoids (C_{21} steroids) and to the androgens (C_{19} steroids). The formation of a substance such as cortisol (hydrocortisone) proceeds from acetate and cholesterol by way of pregnenolone to progesterone. Progesterone is hydroxylated at carbons 11, 17, and 21. Thus, six hydroxylated intermediates are formed which in turn may be converted to cortisol. Aldosterone

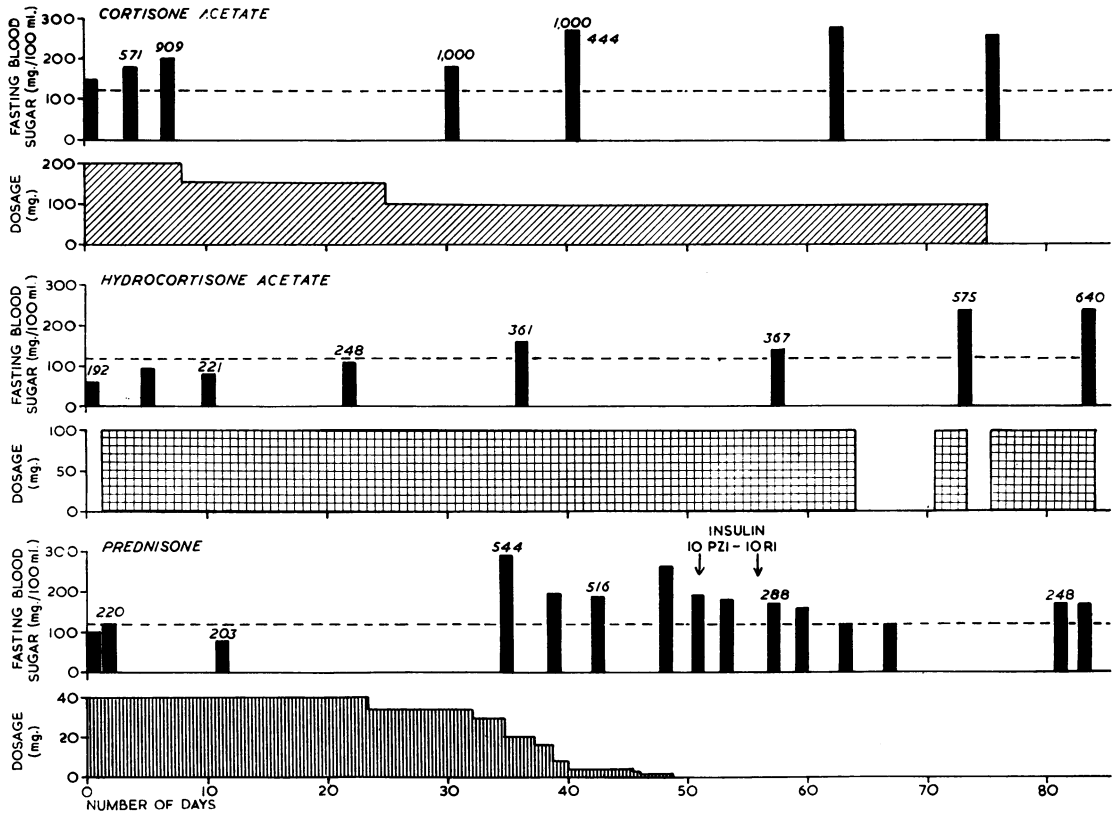


Figure.—Alterations of blood sugar produced by cortisone, hydrocortisone, and prednisone. Vertical bars indicate fasting blood sugar (mg./100 ml.). Figures above some of the bars represent peak blood-sugar values on a 100-g. oral glucose tolerance test.

appears to be biosynthesized by way of progesterone, desoxycorticosterone and 18-hydroxydesoxycorticosterone. The biosynthesis of androgens proceeds from acetate and cholesterol to dehydroepiandrosterone, then to Δ^4-androstene-3, 17-dione, and finally to 11β-hydroxy-Δ^4-androstene-3, 17-dione.

The various adrenocortical steroids are secreted into the blood and catabolized by a variety of enzyme systems in the liver, kidneys, and other organs. The known catabolic changes involve reductive changes at various positions of the steroid molecule such as at carbon 3, 4, 5, and 20, and the oxidative removal of the side chain in some C_{21} steroids forming C_{19} steroids. These products are present in the urine.

MODERATOR BUNIM: To the classical examples of disorders resulting from the presence of C_{21} or C_{19} steroid-secreting tumours in the adrenal cortex which Dr. Dorfman has so clearly described, may now be added a new syndrome, aldosteronism, recently described by Jerome Conn. It is characterized by alkalosis with hypopotassaemia and hypernatraemia, intermittent tetany, muscular weakness, hypertension, and polyuria. There is an excess of aldosterone-like material in the urine, yet the 17-hydroxycorticoid excretion is either normal or only slightly raised. It is believed that this syndrome is associated with adrenal tumours which secrete excessive amounts of aldosterone.

Relation of Chemical Structure to Biological Activity of Adrenal Cortical Steroids including the Halogenated Analogues. By JOSEF FRIED, *New Brunswick, N.J.*

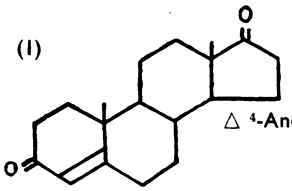
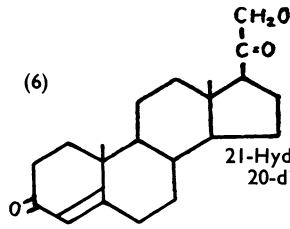
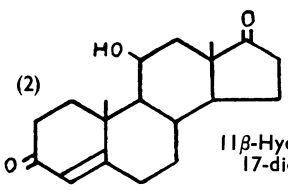
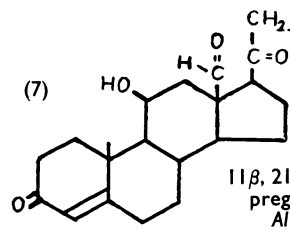
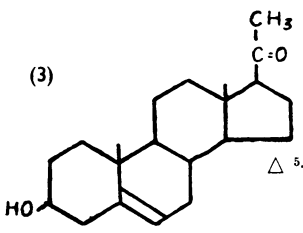
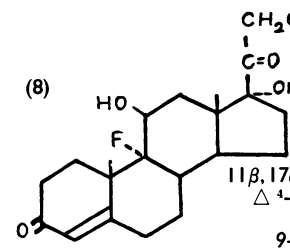
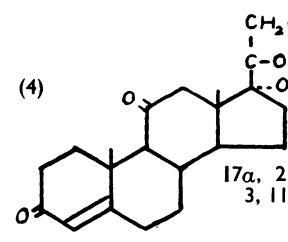
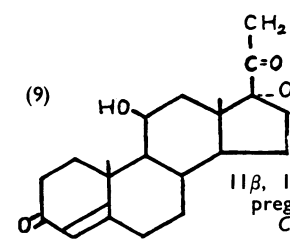
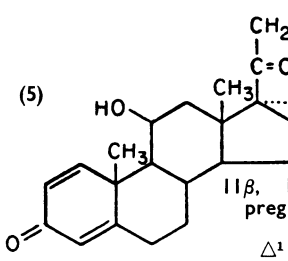
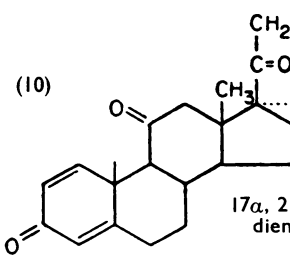
Efforts to enhance the antirheumatic activity and minimize the undesirable side-effects of cortisone and hydrocortisone by modifying the molecular structure of these hormones have until recently met with little success. The conclusion seemed warranted that the structural requirements for an active compound were too exacting to permit chemical modification of the naturally-occurring hormones without complete or partial loss of activity.

The discovery that the introduction of a chlorine and particularly a fluorine atom in the 9-α position of cortisone and hydrocortisone leads to increases in glucocorticoid (cortisone-like), mineralocorticoid (aldosterone-like), and anti-inflammatory activity has made it possible to evaluate the influence of structural changes on the various manifestations of corticoid activity.

The compounds studied by us differ from hydrocortisone and cortisone by the presence of a halogen atom (bromine, chlorine, and fluorine) in the 9-α position, and

TABLE

Nomenclature and Structure of Some Adrenocortical Steroids and Related Steroids

STEROID STRUCTURE	SYSTEMATIC NAME (Common Name)	STEROID STRUCTURE	SYSTEMATIC NAME (Common Name)
(1) 	△ 4-Androstene-3, 17-dione	(6) 	21-Hydroxy-△ 4-pregnene-3, 20-dione *Desoxycorticosterone*
(2) 	11β-Hydroxy-△ 4-androstene-3, 17-dione	(7) 	11β, 21-Dihydroxy-3, 20-keto-△ 4-pregnen-18-al *Aldosterone; Electrocortin*
(3) 	△ 5-pregnene-3β-ol-20-one *Pregnenolone*	(8) 	11β, 17α, 21-Trihydroxy-9α-fluoro-△ 4-pregnene-3, 20-dione *9-α-fluoro cortisol; 9-α-fluoro hydrocortisone*
(4) 	17α, 21-Dihydroxy-△ 4-pregnene-3, 11, 20-trione *Cortisone*	(9) 	11β, 17α, 21-Trihydroxy-△ 4-pregnene-3, 20-dione *Cortisol; Hydrocortisone*
(5) 	11β, 17α, 21-Trihydroxy-△ 1, 4-pregnadiene-3, 20-dione △1 *-Dehydrocortisol; △1 Dehydrohydrocortisone; "Metacortandralone"; Prednisolone*	(10) 	17α, 21-Dihydroxy-△ 1, 4-pregnadiene-3, 11, 20-trione △ 1-*Dehydrocortisone; "Metacortandracin"; Prednisone*

possess side chains varying in their degree of hydroxylation. The following generalizations concerning the relationship between chemical structure and biological activity can be made:

(1) Lowering the atomic weight of the halogen atom leads in all the cases examined to increased glucocorticoid, anti-inflammatory, and mineralocorticoid activity;
(2) In the fluorinated derivatives, substitution of a hydroxyl group for a hydrogen atom in position 21 leads to increases in glucocorticoid, anti-inflammatory, and mineralocorticoid activity. Hydroxylation in the 17-α position causes increases in the first two types of activity and a decrease in the last.

The most active compound of this series, 9-α-fluoro hydrocortisone, possesses ten to fifteen times the anti-inflammatory activity of hydrocortisone. Its high sodium-retaining activity precludes its systemic use in rheumatoid arthritis but not its topical use in dermatology. The fact that specific chemical groupings can cause enhancement of anti-inflammatory and reduction of salt-retaining action points to more potent and less toxic antirheumatic drugs in the future. The meta-drugs (1,2-dehydrocortisone and 1,2 dehydrohydrocortisone) appear to offer the first step in that direction.

Pharmacology and Rate of Metabolism of Hydrocortisone, Cortisone, and Metacortandracin, and the Rate of Synthesis of Hydrocortisone in Man. By RALPH E. PETERSON, *Bethesda, Md.*

We have measured the rate of metabolic transformation of both pharmacological and tracer (Carbon-^{14} labelled) quantities of intravenously administered hydrocortisone, by determining plasma concentrations at several time-intervals after injection. In normal subjects the biologic half-life of this steroid has been found to range from 1½ to 2 hours. The rate of metabolism has been found to be decreased in liver disease, and increased in thyrotoxicosis.

Similar studies have been carried out using cortisone and metacortandracin. Cortisone has been found to be metabolized twice as fast as hydrocortisone and metacortandracin. Data on the rate of excretion of infused hydrocortisone also demonstrates the rapid biotransformation (reduction and conjugation), with 50 per cent. excreted in 3½ hours. The urine contains 80 per cent. of the hydrocortisone metabolites within the first 24 hours, and more than 90 per cent. within the first 3 days. Biliary excretion accounts for but 4 per cent., and more than half of this quantity is eventually excreted in the faeces. More than 99 per cent. of the administered hydrocortisone is transformed by the body to metabolites other than hydrocortisone. Using hydrocortisone 4-C^{14}, we have measured the rate of synthesis of hydrocortisone by the adrenal glands. In normal subjects the adrenal glands produce about 20 mg. hydrocortisone per day. After maximal stimulation with ACTH, the adrenal output was increased approximately ten-fold. In both liver disease and myxoedema the adrenal output was decreased. As part of this same study on steroid production, the miscible pool of hydrocortisone was determined. In the normal it was about 2 mg., distributed in a space slightly larger than the volume of the extracellular fluid.

Effects of Aldosterone, 9-α-Fluoro Hydrocortisone Acetate and Metacortandracin on Rheumatoid Arthritis. By CHARLES H. SLOCUMB, L. EMMERSON WARD, HOWARD F. POLLEY, and PHILIP S. HENCH, *Rochester, Minn.*

Aldosterone was administered to two rheumatoid patients for six days each, in doses up to 800 μg. per day in one patient and 1,000 μg. per day in the other. These doses produced no antirheumatic effects, but did produce retention of sodium, chloride, and fluid.

9-α-fluoro hydrocortisone acetate was administered to three rheumatoid patients in doses up to 4, 6, and 8 mg. daily for 12 to 28 days. These comparatively small doses lessened rheumatic symptoms, but produced troublesome retention of sodium chloride and fluid, and loss of potassium. The changes were sufficient to cause oedema and hypopotassaemia with a tendency for the development of hypochloraemia and alkalosis.

Metacortandracin was administered to two patients for up to 24 days in dosages of up to 30 mg. a day. This dosage lessened rheumatic symptoms, and there was no significant excess sodium or chloride retention or potassium loss, although the patients were in negative nitrogen balance.

MODERATOR BUNIM: The next and last panellist is Dr. Edward Boland, whose presidential address forms part of this survey of progress in the development and trial of these steroids and their analogues.

Preliminary Clinical Experience with Metacortandracin in Rheumatoid Arthritis. By EDWARD W. BOLAND, *Los Angeles, Calif.*

Clinical observations were made of the effects of metacortandracin (Δ^1-dehydrocortisone) in 52 patients with active peripheral rheumatoid arthritis, treated uninterruptedly for periods of 3 to 5 months. The study, which is still in progress, was designed to determine:

(1) The effects of the compound when given as initial therapy;
(2) Dosage schemes for its practical application;
(3) The relative antirheumatic potencies of metacortandracin and hydrocortisone;
(4) The therapeutic efficiency of metacortandracin as compared to that of hydrocortisone on continued administration.

Group 1.—The response to metacortandracin employed as initial therapy was observed in eleven patients. Suppressive doses were varied with the severity of the disease and ranged from 15 to 30 mg. a day. Prompt and striking antirheumatic effects resulted in ten patients, the pattern of improvement being similar to that noted with hydrocortisone and cortisone given in larger suppressive amounts. Subjective relief began within 3 to 72 hours of the first divided dose, and objective improvement was noted within 2 to 7 days. Adequate suppression of the disease was achieved in nine patients after 7 to 21 days of administration. With daily main-

tenance doses ranging from 7·5 to 25 mg., major improvement was maintained for 3 to 5 months in nine patients. One or more adverse signs appeared in seven patients; these were minor in five, but sufficient in the other two to cause limitation of dosage below optimally effective levels.

Group 2.—Estimates were made of differences in antirheumatic potency between metacortandracin and hydrocortisone in fourteen patients. This was accomplished by transferring patients whose disease was adequately, but not completely, controlled on established stable maintenance doses of hydrocortisone to treatment with the new compound. In each instance the dosage of metacortandracin required to maintain approximately an equivalent degree of improvement was smaller. Dosage ratios of metacortandracin to hydrocortisone varied from 2·4 : 1 to 5·3 : 1 (average 3·97 : 1). Later the dosage of metacortandracin was increased above equivalently effective amounts, and in thirteen of the fourteen patients greater benefits were provided and maintained.

Group 3.—27 patients whose clinical control was unsatisfactory while being maintained on hydrocortisone, were transferred to treatment with metacortandracin. In 25 the immediate results were favourable; major improvement was achieved or restored with smaller, but more effective, doses of the new steroid.

After 3 to 5 months of continuous metacortandracin therapy, sixteen of the 27 patients (59 per cent.) were classified as adequately improved. In general, the percentage of patients demonstrating satisfactory control fell as treatment was prolonged: improvement was considered as adequate in 74 per cent. after 1 month, in 89 per cent. after 2 months, in 78 per cent. after 3 months, in 58 per cent. after 4 months, and in 50 per cent. after 5 months. Nine patients responded well at the beginning, but later deteriorated because responsiveness to the drug diminished and because side-effects intervened to a degree which forbade further increases in dosage. The dosages of metacortandracin varied from 7·5 to 30 mg. a day (average 16·7 mg.).

24 patients exhibited one or more hormonal complications, total 87 effects. After 3 to 5 months all 27 displayed unwanted reactions, total 94 effects. 27 side-effects disappeared, eight lessened in degree, 24 remained unchanged, and 28 became more pronounced. 34 "new" signs developed during administration of the new analogue, many of which were cumulative. Although most of these reactions were mild or moderate in severity, they were troublesome enough in ten patients to limit dosage and prevent satisfactory results.

These short-term observations indicate that metacortandracin has certain advantages over hydrocortisone in the treatment of rheumatoid arthritis, consisting mainly in the absence of salt-and-water retention with ordinary therapeutic doses, the capacity to restore adequate improvement in patients who have lost satisfactory control after prolonged hydrocortisone administration, and the ability to maintain the greater benefits in a significant percentage of such patients for periods up to 5 months, at least. However, the other difficulties and potential hazards encountered with the older steroids seem to be shared by the new derivative. Indeed, some adverse reactions, notably digestive complications, ecchymotic skin lesions, and vasomotor symptoms, have occurred more frequently and have been more troublesome with the new analogue.

Metacortandracin is thus, far from an ideal suppressive agent for rheumatoid arthritis, but it possesses some important refinements—and its discovery strengthens our conviction that, through further permutations of chemical structure, steroids with higher therapeutic efficiency may be developed in the future.

MODERATOR BUNIM: I will take the liberty of paraphrasing an especially lengthy question:

What is Dr. Dorfman's opinion of the comparative merits of different methods of measuring the relative potency of the biologically active steroids?:

(1) Its inhibitory effect on the pituitary as reflected by the reduction of 17-hydroxy steroids in the urine; by a decrease in the 17-ketosteroids in the urine; and by a decrease in the 17-hydroxycorticosteroids in the blood or plasmas;
(2) Its suppression of the endogenous production of hydrocortisone by the adrenal cortex as measured by the method described by Dr. Peterson.

DR. DORFMAN: Inherent in the question is the idea that there may be a correlation between the activities of a steroid by the different procedures named. If we are going to talk about relative merits we must ask if the different methods measure comparable activity, and it is doubtful whether this is so. Let us first consider pituitary inhibition and urinary steroids. Since 17-ketosteroid and 17-hydroxycorticoid (and I presume that the speaker is referring to the tetrahydro derivatives of cortisol and cortisone) excretion in urine is not always correlated under all physiological and pathological conditions, it would be presumptuous to assume, without adequate studies, that a correlation need exist. In short, one cannot choose between the indices, one can only suggest more studies whereby the various compounds are studied under comparable conditions by all the methods mentioned and perhaps even others.

MODERATOR BUNIM: Another question, sent to Dr. Fried, read something like this:

What would give you the best or the most reliable and direct correlation between the anti-inflammatory effects of a steroid and the following physiological tests:

(1) glycogenic deposition in the adrenalectomized rat;
(2) thymic involution;
(3) eosinophilic response;
(4) direct anti-inflammatory effect by cotton pellets in the rat?

DR. FRIED: We have used these four methods and I would say the quantitative correlation is about equally good for all of them with the exception of the thymic involution assay, which appears to be less specific. There are a number of substances that will cause thymic involution, but will not show liver glycogen deposition. The liver-glycogen test in the rat is a very accurate and economical test if properly carried out, and so is the cotton-pellet test for anti-inflammatory activity. We like these two methods, and so far the correlation is good.

Unfortunately, we do not know the antirheumatic activities in man of all the more active steroids discussed here and it would be very desirable, although some of these compounds may have undesirable side-effects, to

test them for their anti-arthritic effects, and to find out whether the correlation established in experimental animals is the same in man. Of the limited number of compounds that have been tested for their anti-arthritic activity in man, both the liver glycogen and the anti-inflammatory activity in the rat were paralleled.

MODERATOR BUNIM: Dr. Peterson, by the method of measuring the miscible pool and the rate of secretion of hydrocortisone, how does the potency of metacortandracic compare with that of hydrocortisone and cortisone; or did you not do those determinations?

DR. PETERSON: We have only done this in one case and with meticorten, so I have no data on the relative potency of the three steroids by this method.

MODERATOR BUNIM: Dr. Slocumb, please discuss briefly osteoporosis occurring in steroid administration.

DR. SLOCUMB: Dr. Bauer's group gave you more information than we have to-day. The short-term metabolic studies with these steroids have not given us a real answer as to the calcium metabolism compared with what we see clinically. Clinically, we feel that osteoporosis is produced by cortisone and hydrocortisone and undoubtedly by metacortandracin, but this comes after rather long administration and by adding to the tendency of the disease to produce osteoporosis.

The incidence of fractures, certainly of compression fractures, is certainly higher than we should expect in rheumatoid arthritics.

MODERATOR BUNIM: Should testosterone be used for its non-specific antibiotic effect in long-term therapy?

DR. SLOCUMB: I think it should be tried. It will certainly help with such things as nitrogen retention. We want to know about the appearance of all the side-effects of these hormones and are trying to find the safest way of administering them, so we are not adding testosterone, oestrogens, or the other things at this time.

MODERATOR BUNIM: Dr. Boland, is it necessary in the administration of metacortandracin: (*a*) to restrict sodium intake, (*b*) to supplement with potassium salts.

DR. BOLAND: Although metabolic studies performed by Dr. Bunim's group and by others indicated that metacortandracin in dosages of 30 mg. a day or less causes little or no alteration in sodium or potassium excretion, we approached the problem cautiously. Among our early patients extra salt, that is, amounts over and above that used normally in cooking, was denied. In later cases we became more liberal and at present most of our patients are on a regular diet and are not restricted in their salt intake. So far oedema resulting from salt retention has not been a problem, and we have found no need for complemental potassium salts or other diuretic agents.

MODERATOR BUNIM: Please compare metacortandracin and metacortandralone in simple application.

DR. BOLAND: We have now had experience with metacortandralone in well over 75 patients with rheumatoid arthritis. So far we can see little difference between metacortandralone and metacortandracin in regard to antirheumatic potency or adverse effects. The two substances have been found to be interchangeable, and differences, if they do exist, must be very small.

MODERATOR BUNIM: Here is a question which I cannot direct to any specific member of the panel. I am inclined to call on a volunteer from the audience: "May it not be possible that many of the ill effects and apparent inadequacies of the steroids may be due to an effect on the basic immune mechanism? If so, what future can be expected from this direction?"

DR. BOLAND: I doubt whether any member of the audience is bold enough to attempt to answer this!

MODERATOR BUNIM: Another question directed to Dr. Boland: "To reduce the side-effects of meticorten, is it advisable to combine 50 per cent. of hydrocortisone with 50 per cent. of Meticorten?"

DR. BOLAND: The practical management of patients with both hydrocortisone and metacortandracin is so complex that we have not had the temerity, nor have we seen reason, to use them in combination.

MODERATOR BUNIM: Another question for Dr. Slocumb: "What measure can you employ to counteract the decalcifying effects of corticosteroids?"

DR. SLOCUMB: We keep the dosage down and our patients ambulatory. We have not found it necessary, with the small dosage, to give calcium or aluminium salts.

If there is compression, we start gradual reduction, see that the back or area in question is properly supported, and get the patient active again as soon as we can, that is within a week or so.

DR. BOLAND: I should like to ask Dr. Fried and Dr. Dorfman together—and to get this answer was one of the objects of this symposium: Do you think it possible to develop a substance with antirheumatic activity and to get the bugs out and to get the side-effects out of it in the future? Dr. Fried?

DR. FRIED: Studies of the various hydrocortisone analogues show that some of the metabolic actions of hydrocortisone (such as its effects on carbohydrate, protein, lipid, and electrolyte metabolism) can be intensified or reduced independently of each other. In other words, a certain alteration in chemical structure may potentiate one metabolic effect, diminish another, and leave a third unaffected. This may be interpreted to mean that each metabolic effect has its own specific structural requirements.

Now if you accept that premise, you may justifiably conclude that it is theoretically possible to create a substance that causes only the effects that you require and none that you do not. More knowledge of the relationship between structure and activity is necessary.

DR. DORFMAN: Concerning the intensification of desirable properties and the minimizing of unfavourable properties in "tailor-made" steroids, we have recently seen very striking successes, not only in the separation of carbohydrate and protein activity from electrolyte effects, but even in modifications of the relative sodium and potassium effects in some of the newer compounds. If such divergencies can be produced, further effort may bring us closer to the realization of more ideal thera-

peutic agents. In this field, industry, through the efforts of workers like Dr. Fried, is showing us the way.

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FIVE PAPERS PRESENTED IN CONJUNCTION WITH THE AMERICAN COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

(1) Isolation and Characterization of the Non-Specific Hyaluronidase Inhibitor of Human Blood. By GERALD S. BERENSON, JOYCE K. NEWMAN, MARTIN B. MATHEWS, and ALBERT DORFMAN, *Chicago, Ill.*

Previous studies have demonstrated the presence of a substance in the blood of humans and other mammalian species which inhibits the enzyme hyaluronidase. One of the changes occurring in blood during the acute phase of rheumatic fever and other inflammatory conditions involve an increase in the level of the non-specific hyaluronidase inhibitor. The lability and its invariable presence, irrespective of a previous exposure to hyaluronidase, suggest that this substance differs from specific antibodies to hyaluronidase. More recently, attempts have been made to add to information concerning the nature of this substance. This report deals with the isolation and characterization of the inhibitor.

By means of a purification procedure (involving alcohol fractionation, precipitation at low ionic strength, and zone electrophoresis on a starch slab), a material with hyaluronidase inhibitory activity was isolated with a purification up to approximately 1,000-fold over plasma. Preparations so isolated appeared to be essentially monodisperse on ultracentrifugation, free solution electrophoresis, and diffusion studies. The molecular weight was calculated to be about 100,000. The sedimentation constant $S_{20} = 3{\cdot}7$ S and mobility in a veronal buffer, pH 8·6, $\mu 0{\cdot}1 = -5{\cdot}4 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ volt.$^{-1}$ Chemical analysis showed the following composition (per cent.):

N	14·4
Polypeptide content	75
Hexosamine	4
S	< 0·1
P	0·2
Tyrosine	2·7
Tryptophane	0·9

A positive test for hexuronic acid was obtained by the carbazole method and a qualitative amino acid composition, by means of paper chromatography, indicated the presence of twelve to fourteen different amino acids.

(2) Immunological Evidence of Group A Streptococcal Infection in Patients undergoing Mitral Commissurotomy. By W. F. LYNCH, G. H. STOLLERMAN, M. A. DOLAN, D. YOUNG, and J. B. SCHWEDEL, *New York, N.Y.*

Forty-five patients undergoing mitral commissurotomy for mitral stenosis were studied to determine whether antecedent group A streptococcal infection was related to

(*a*) histological findings in the biopsied auricular appendage;

(*b*) the post-operative development of clinical manifestations suggesting reactivation of rheumatic fever.

Serial determinations of the serum titres of antistreptolysin O, antihyaluronidase, and antistreptokinase were made pre-operatively and each month during a post-operative period of at least 3 months. Throat cultures were made at monthly intervals in most cases, and wherever possible prophylaxis against intercurrent streptococcal infection was maintained.

Of the 45 patients studied, 36 were found to have low serum levels (below 200 units/ml.) of all three antibodies immediately before operation. Of these patients, in whom recent pre-operative streptococcal infection was not apparent, five were found to have characteristic Aschoff nodules in the biopsied auricular myocardium. In four others the histological findings were suggestive of rheumatic myocarditis. In nine, immunological evidence of recent streptococcal infection was found pre-operatively; of these, one had typical Aschoff nodules in the biopsied auricular appendage and two had lesions suggestive of rheumatic myocarditis.

Eight patients developed manifestations suggestive of the "post-commissurotomy syndrome". In two of these there was no immunological evidence of streptococcal infection pre- or post-operatively. In the remainder, three had high levels of antibodies before operation and three others showed a significant rise in antibody during the post-operative period before the onset of the post-commissurotomy syndrome.

The data indicate that Aschoff nodules may often persist in the myocardium without immunological evidence of recent streptococcal infection being obtained by the methods employed. It also appears, however, that streptococcal infection is relatively common post-operatively (it occurred in twelve of 45 patients) and may be among the factors influencing the post-operative course, particularly the reactivation of rheumatic fever.

Discussion.—DR. ARNOLD LIEBERMAN (*Northport, Long Island, N.Y.*): How long after surgery do you advocate continuing your prophylaxis?

DR. LYNCH: We did not determine that point; we arbitrarily took a period of 3 to 4 months after surgery, but have reached no conclusions on how long prophylaxis should be continued post-operatively.

(3) Changes in Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase, in Rheumatic Fever (Preliminary Report). By IRWIN NYDICK, JAMES TANG, GENE H. STOLLERMAN, FELIX WROBLEWSKI, and JOHN S. LA DUE, *New York, N.Y.*

A simple, accurate, spectrophotometric test for the analysis of the serum concentration of the enzyme, glutamic oxalacetic transaminase (SGO-T) has been previously devised. Studies have shown this enzyme to be most concentrated in heart muscle and to rise precipitously in the serum following myocardial necrosis in man and experimental animals. The theoretical and clinical importance of testing for necrosis of the myocardial fibre, *per se*, in rheumatic fever is the basis of the present study of 64 rheumatic subjects in all stages of the

disease. Of 26 patients with active carditis, seventeen were found with abnormal serum levels; of eighteen "inactive" patients with a definite recent or past history of carditis, all sera analysed were within normal limits. Of twelve patients with non-cardiac rheumatic manifestations, only one developed abnormal serum concentrations of SGO-T, and this patient subsequently developed equivocal signs of an active carditis. Eight rheumatic subjects who developed virus pneumonia were studied, and in one an evanescent, slight elevation of SGO-T occurred when the EKG showed grossly abnormal T-waves, probably the result of the mild myocarditis occasionally seen with virus pneumonia.

There was no obvious relationship of the SGO-T to levels of the various "acute phase reactants". When the erythrocyte sedimentation rate, C-reactive protein, and white blood count were normal during antirheumatic therapy, there were often striking rises in SGO-T. The clinical course of carditis did not consistently parallel fluctuations in the enzyme levels. Some patients with severe carditis and congestive heart failure had normal levels; others with low-grade carditis were seen with five-fold increases. Aspirin and steroid therapy had variable relationships to changes in the SGO-T.

A microscopic study of auricular appendages (operative specimens) was undertaken in twelve patients and tissue obtained at autopsy was available in three. The SGO-T was abnormal at some time in five or ten patients with at least one of the following microscopic signs of inflammation: Aschoff nodules, round-cell infiltrations, acute myocardial cell necrosis, fibrinoid degeneration of collagen. Of the five patients with no microscopic evidence of inflammation, only one showed an elevation of the SGO-T, and in this patient extensive fibrous replacement of myocardial fibres was seen at autopsy.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va.*): Is there definite evidence that skeletal muscle wasting, such as one sees in chronically ill patients merely lying in bed, does not elevate the SGO-T, and more particularly whether this might not occur in muscle-wasting myopathies such as thyrotoxic or rheumatoid myopathy.

I gather that it is your impression that, though infractions of the liver may give rise to elevated SGO-T, this does not occur in acute passive liver congestion.

DR. NYDICK: We studied a large number of chronically debilitated patients with generalized carcinoma at the Memorial Hospital. Muscle wasting is often a prominent feature of their disease. In general, these patients did not have transaminase elevations unless the liver was involved by metastases.

We studied SGO-T levels in degenerative myopathies but did not follow the course of the transaminase over long periods; those that we followed for a few days to a few weeks were normal, but during the active phase of dermatomyositis in two patients, elevations of the transaminase occurred, which were presumably due to acute skeletal muscle necrosis.

Two patients with marked thyrotoxicosis had normal transaminase activity although they had clinical and laboratory evidence of severe thyrotoxicosis associated with marked muscle weakness; 28 patients with passive congestion of the liver failed to develop increased SGO-T. In two of these latter, moderate elevations were noted in acute shock-like episodes in the course of the congestive failure. These may have reflected liver injury due to anoxaemia and were perhaps caused by areas of hepatocellular necrosis such as have been reported after shock.

DR. HARRY A. FELDMAN (*Syracuse, N.Y.*): The authors were wise to label this a preliminary report, because it appears that this problem requires a good deal more study. In recent weeks, Dr. Lionel Rudolph of our department has measured the serum transaminase content of five patients with acute rheumatic fever and active carditis, and in only one of them was a level as high as 44 units found. This was in a patient who had two determinations; first 22 units and a week later 44, a change of only questionable significance.

One of the five patients died and was found to have gross evidence of acute rheumatic pancarditis at autopsy. She had had a level of 8 units 2 days before death. In the microscopic sections there is evidence of widespread myocardial involvement.

I have made some calculations from the data presented and it comes out that in the group with congestive failure and active carditis, some 19 per cent. of determinations—not patients—were abnormal.

In the group which was thought to have rheumatic heart disease and active rheumatic fever without carditis, 20 per cent. of the determinations were abnormal. In the group with polyarthritis (admittedly only one of these patients had any abnormal measurements), abnormal levels were encountered in 21 per cent. These three different clinical groups therefore show approximately similar frequencies of abnormal serum transaminase levels.

DR. NYDICK: In the five patients studied by Dr. Rudolph, very few serum glutamic oxalacetic transaminase determinations were done. I think that this is critical because in our group of patients, sera were obtained three times weekly, and it is obvious that the course of the serum transaminase may be very variable during rheumatic carditis, so that it would be easy to miss occasional peaks. For example, in two of the children it rose as high as 200 units, but had we skipped that particular week we should have missed the peak as well as the subsequent abnormal concentrations. It is essential to obtain sera frequently while studying the course of transaminase in rheumatic fever. Rheumatic fever is primarily an inflammatory process in collagenous tissue and the ground substance. It would be surprising if myocardial necrosis continued throughout the entire course of rheumatic carditis. It seems more likely (and this is what we should like to infer from our data) that during the course of the interstitial inflammatory process in the heart, myocardial necrosis may supervene; at that time the transaminase may rise and thus reflect the myocardial fibre involvement, not necessarily the interstitial inflammation.

We believe that our analysis of the percentage of abnormal results was valid for three reasons. First, 14 per cent. of the total number of determinations in the first two groups of patients ("definitely active carditis" and "questionably active carditis") were abnormal, as contrasted with 4 per cent. in all the other groups. Second, 65 per cent. of all the patients with carditis revealed abnormalities in the SGO-T at some time during their course as contrasted with the other groups, in which only 4 per cent. of the total developed elevations at any time. Finally, if one excludes the one patient with polyarthritis who was discussed in detail, and in whom equivocal evidence of carditis was present, only one

abnormal result was obtained in over three hundred sera analysed in the entire group of patients without known active carditis, *i.e.* convalescent rheumatic patients, patients with chorea, rheumatoid arthritis, erythema marginatum, and rheumatics who developed virus pneumonia. We believe that analysing the data in this fashion would make it more statistically significant.

(4) Relation of Incidence of Heart Damage in ACTH- and Cortisone-treated Rheumatic Fever to Dosage and to Duration of Illness. By SUJOY B. ROY and BENEDICT F. MASSELL, *Boston, Mass.* (By invitation.)

Of 140 rheumatic fever patients (under 17 years of age) in initial attacks, 56 (Group A) were treated for 6 weeks with a total of 4·1 g. cortisone or 1,100-2,500 units ACTH, and 84 (Group B) were treated for 12-16 weeks with a total of 13-15 g. cortisone or 4,100-7,000 units ACTH. Group A included the patients contributed by the House of the Good Samaritan to the Cooperative Rheumatic Fever Study.

On discharge from the hospital, heart damage was present in 70 per cent. of Group A (small dose) and 38 per cent. of Group B (large dose). Incidence of heart damage was also related to the duration of illness. Thus, for duration sub-groups the incidence of heart damage was as follows:

Days	Group	
	A	B
0– 7	30	19
8–14	69	24
15–42	80	45
Over 42	100	79

The frequency with which significant murmurs, present at the beginning of therapy, disappeared was 20 per cent. in Group A, and 40 per cent. in Group B. This incidence was also related to the duration of illness. Thus the incidence of disappearance of significant murmurs was as follows:

Days	Group	
	A	B
0– 7	50	62
8–14	25	43
15–42	13	40
Over 42	0	17

Groups A and B with significant murmurs at start of therapy were comparable regarding such important manifestations as cardiac enlargement, pericarditis, congestive failure, and subcutaneous nodules.

The data, though not conclusive, strongly suggest that good results of hormone therapy are dependent on prompt treatment with relatively large doses, given over a relatively long period.

Discussion.—DR. DENNISON YOUNG (*New York City*): This problem bothers us all constantly. Dr. Roy and Dr. Massell have had considerable experience for many years with this disease. What can they tell us about the incidence of carditis in a comparable group of patients treated within the last 2 years with bed rest alone?

DR. EDWARD E. FISCHEL (*New York City*): It seems almost axiomatic that any disease will do better the earlier we treat it. I think this very point "discoloured" the therapy of rheumatic fever with salicylate for many years; people failed to consider that groups with and without therapy of any kind should be compared with similar groups as regards duration of active disease before the observation period.

In the Cooperative Study the duration of illness before therapy was a significant factor in the outcome, perhaps more so than the kind of drug used.

I do not like to be characterized as a member of the pessimistic group that felt that the hormones were, at the most, no better than aspirin. We were optimistic enough to think that both drugs do good if given early, in large dosages, and for a fairly long time.

DR. ROY: In reply to the first question of Dr. Young, we have not yet got all the data ready, but we have enough evidence to state that before the introduction of hormone therapy, young children admitted with acute congestive failure used to die like flies.

I feel honoured that Dr. Fischel has spoken, for I thought his paper on long-term salicylate administration* was very good. I come from a poor country where we had to use salicylate, unless some foreign firms gave us free hormones.

His statement is complementary to what we have said, we did not mean to suggest that aspirin is a better drug than the hormones or not. We were just trying to submit, very humbly, that divergent opinions on this subject may in part be due to not taking the duration of the illness and the size of the dose into consideration. I know that a very famous lady sitting here believes you do not have to give it for a long time, and that 7 days is probably long enough. We haven't tried it, but she finds wonderful results, and I see no reason why others should not do the same.

DR. MAY G. WILSON (*New York City*): I am very happy that it has finally been impressed upon a great many people that it is important to treat early, and important to treat with a large enough dose. I hope by next year to hear that you do not have to give it so long.

(5) Effect of Intensive and Prolonged Cortisone and Hydrocortisone Therapy in First Attacks of Rheumatic Carditis. By MILTON MARKOWITZ, *Baltimore, Md.*, and ANN KUTTNER, *New York City.* (By invitation.)

Cortisone is an effective agent for the suppression of the inflammatory reaction caused by rheumatic fever, but whether cardiac damage is prevented or diminished by the suppression of inflammations is not known. Greenman and his co-workers reported a low incidence of residual heart disease in patients developing carditis during their first rheumatic attack treated early with large daily doses of oral cortisone. In view of these findings, further studies of the effect of large doses of cortisone or hydrocortisone were undertaken.

Forty patients with first attacks of rheumatic fever with clinical evidence of carditis were treated. All received either 200 or 300 mg. oral cortisone or oral hydrocortisone daily for 6 weeks. In eighteen of these patients, the

* Fischel, E. E. (1952). *Medicine (Baltimore)*, 31, 331.

dosage was then tapered over a 3-week period. In the remaining 22, after 9 weeks of therapy, a maintenance dose of 50 mg. cortisone daily was continued for 2 to 10 months. Patients with exacerbations of carditis after the termination of therapy were re-treated with 50 mg. cortisone daily for 4 to 8 weeks.

Of these forty patients, 29 received treatment within 3 weeks or less of onset. After follow-up observations ranging from 6 to 22 months, 24 of these 29 patients have no evidence of heart disease. Patients with severe as well as mild carditis responded equally well.

Eleven patients treated later than 3 weeks after onset did less well. Only two have normal hearts; eight have rheumatic heart disease and one has died.

Apart from minor signs of the Cushing syndrome, eleven of the forty developed undesirable side-effects.

The results suggest that cortisone, given early in the course of the rheumatic attack in large doses and continued until the disease has run its course, may reduce the incidence of residual heart disease.

Discussion.—DR. HARRY A. FELDMAN (*Syracuse, N. Y.*): I believe we are witnessing something of the completion of a cycle. Several years ago we heard a great deal of discussion about the reversibility of the acute rheumatic lesion or the reversibility of rheumatoid arthritis as a result of steroid therapy.

Given treatment at a certain (but as yet undefined) stage of active rheumatic fever, one cannot expect *total* reversion to a normal tissue state, but, given adequate treatment at the proper time, one may expect substantial reversion to the pre-attack state in many patients.

The question should be, what is "adequate" dosage? It makes no difference whether the dose is "large" or "small". We have to administer a certain amount of a given drug in order to obtain an optimal therapeutic response, and we should know what those amounts are; I think we should speak in terms of "adequate" rather than of "high" or "low" doses.

The patients who died during therapy are of special interest; if one examines such cases as reported in the literature, it seems that most of these seem to be patients who were started on steroid therapy rather late in the course of their acute rheumatic fever. I don't quite understand this, and it would be of interest for some of us to keep watch on this to determine whether this is more than just an impression.

In our own hospital we have recently had such a death. Treatment was started in the sixth week of the illness and the patient died some 5 or 6 days later. There may have been no causal relationship, but I believe that I have encountered three such cases in the literature, and there was also one in the paper just presented by Dr. Markowitz.

Having said that, I shall proceed to discuss our own experiences (in conjunction with Dr. Leo Jivoff) with prednisone* in the treatment of acute rheumatic fever. We have treated ten such patients in recent months, each of whom had active carditis; six were children and four were adults. Our dosage schedule was set up like this:

First day 50 mg. in four 6-hrly doses.
Second day, dose reduced to 40 mg.
At 96-hr intervals, depending upon maintenance of clinical improvement, dose decreased by 5 mg. daily.

* Supplied by the Schering Corporation.

We found that the usual symptomatic response was rather good with this dosage schedule. The temperature dropped to normal within hours, and joint pain was relieved rather quickly, but signs of joint effusion lingered in most patients for 4 to 5 days. The C-reactive protein reverted to normal usually in 7 days with the erythrocyte sedimentation rate somewhat more slowly.

The anaemia, when present, corrected itself rather promptly, so that by the 8th to 10th day, there was usually a very noticeable improvement in both the haemoglobin and haematocrit. None of these patients was on a sodium-restricted diet and there was no evidence of abnormal water-retention.

Because five of these patients required re-treatment on this schedule, it appeared to us that we might not be giving sufficient medication. When another patient came in with severe carditis, we decided to increase the dose to 100 mg. initially and then drop to 90 mg.—in other words, to double the previous schedule. On the 6th day of therapy this patient developed frank congestive failure, and withdrawal of the drug led to diuresis and clearing of the failure. The carditis did not seem to be benefited, but it had been present for some weeks. This experience suggests that in doses such as these sodium had better be restricted, even with prednisone.

Five patients developed mooning of the face and in three acne appeared in 10 to 14 days.

One patient died (whom I mentioned earlier) and at autopsy was found to have active pancarditis. She also had chorea and some bronchial pneumonia.

One patient developed staphylococcal pneumonia which went on to abscess formation but resolved satisfactorily when the steroid was withdrawn and antimicrobial and salicylate therapy instituted.

In ten patients, then, with acute rheumatic carditis on the dosage schedule described, the response was generally good; I think that prednisone deserves considerably more study, but as yet we have no notion of what constitutes adequate dosage.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): These two papers, by Drs Roy and Massell and by Drs Markowitz and Kuttner, are of extraordinary importance. Their observations can readily be reconciled with evidence obtained experimentally. From tissue culture and the animal studies reported by Leon Weiss, it becomes evident that there is a phase in the development of the inflammatory process at which the mononuclear cell, derived from either the circulating blood or connective tissue, becomes transformed into a macrophage. As this transformation occurs, the macrophage acquires both adaptive and constitutive enzymes. Moreover, monocytes may then fuse into multinucleated giant cells.

It is therefore conceivable that when an anti-inflammatory agent, such as cortisone, hydrocortisone or prednisone, is administered, it may, if given early enough, cause a recession of the inflammatory process at such a strategic time as might inhibit the transformation of the mild-mannered monocyte to the more aggressive and predatory macrophage.

Let us add to this observation the results reported by Thomas Dougherty, who induced inflammation in the subcutaneous tissue of mice by injecting standard doses of phlogistic substances, such as histamine-diphosphate, pyrogen or gelatin, and 6 hours later counted the inflammatory cells totally and differentially. This affords a reliable means of measuring the degree of inflammatory response and correspondingly the anti-phlogistic potency of various anti-inflammatory agents. Dougherty found

that cortisone and, to a much greater degree hydrocortisone, possessed anti-phlogistic properties. It should be emphasized that he also established a correlation between the size of the dose and the anti-inflammatory effect of the steroid. Thus it becomes evident from experimental observations that time and dose are both extremely important factors.

In closing, I should like to add that in a joint study with Dr. Markowitz and Dr. Charlotte Ferencz of Johns Hopkins University, we have studied the clinical and metabolic effects of large doses of prednisone in thirteen children treated during the first 26 days of initial attacks of acute rheumatic carditis. Thus far, nine have been treated for at least 5 weeks. Unequivocal organic murmurs present before therapy have already disappeared in seven of the nine patients, and these seven children now have no signs of organic heart disease. All but one of the patients in the series are still receiving prednisone, which we plan to give for no less than 14 successive weeks. None of the patients developed oedema, sodium retention, hypokalaemia or congestive heart failure, yet all were on unrestricted sodium.

DR. CURRIER MCEWEN (*New York City*): I am glad that Dr. Feldman made the comment he did that one should use "adequate" suppressive dosage and not think of dosage in terms of "small" or "large". It seems to me that it should be possible as time goes on to adopt as the guiding principle, not a given size of dose for a certain number of weeks until the attainment of certain effects, such as the disappearance of gallop, heart failure, tachycardia, and laboratory evidence of inflammation, and to use doses large enough to achieve these effects as required by the individual patients.

I think we may probably accept to-day that if a patient is treated early with a drug that is capable of suppressing rheumatic inflammation, the results are hopeful; in that sense we are far better off than we were 5 or 10 years ago, when we felt that none of our suppressive drugs really had much effect on the carditis.

The question whether cortisone or other steroids are superior to salicylates in that suppressive action remains unsettled. I think most of us would consider the steroids more potent in antirheumatic suppressive power than the salicylates, but I suspect most of us would agree to-day that the difference is probably merely one of degree. Finally, in connexion with Dr. Fischel's remark about the good effects obtainable with salicylates, we should not forget this tried and true agent, and I should like again to support the view that salicylates and steroids may advantageously be used together.

DR. MORRIS ZIFF (*New York City*): My question concerns the time interval before one institutes cortisone. Does a waiting period eliminate some of the mild cases so that one obtains poorer results with the remaining group? Could this explain the less favourable results the longer one waits to start therapy?

DR. MARKOWITZ: I think that is an important point. I think Dr. Ziff knows the answer to it, because some of these patients were from his group. We should like very much to wait 24 to 48 hours; despite the fact that we advise early therapy, we do not like using this involved and even risky treatment unnecessarily. So that waiting 24 to 48 hours in such a patient and making certain of carditis and, indeed, of the degree of carditis, would seem to me to be very much in order.

It has been the custom in some places to give aspirin for 24 to 48 hours and so reduce the fever; often a striking reduction in tachycardia and a striking improvement in heart sounds indicates that carditis is absent and hormone therapy not indicated. We feel very strongly, at present, that hormone treatment should be limited to patients with very clear-cut carditis.

DR. ROY: In Boston we are carrying out a study which is comparable with the Cooperative Study except that we are dealing with a larger amount of cortisone or ACTH, and that the criteria are exactly those of the Cooperative Study. We are really not waiting, but trying to catch cases as early as possible. So far, we have been very lucky in that we have not many side-effects. We lost one patient with chicken-pox.

Dr. McEwen's suggestion that we use the term "adequate suppressive dosage", is very good. We showed "small" doses and "large" doses to illustrate our point; what we really are talking about is an "adequate" dose.

We believe aspirin has a suppressive effect, and the answer will come when we get enough cases to analyse. We have only about ninety cases so far, but we expect another hundred in the next year, and then maybe we shall be able to say more about it.

* * * *

Course of Severe Rheumatoid Arthritis during Four Years of Induced Hyperadrenalism. By DAVID S. HOWELL, *New York, N.Y.* (Introduced by Dr. Charles Ragan.)

68 patients with rheumatoid arthritis have received cortisone, ACTH or hydrocortisone during a period of 6 months to 5½ years. The duration of disease was 3 years or longer in 90 per cent. of the series and 61 patients exhibited advanced arthritic lesions by *x* ray (Stages 3 and 4 by the Steinbrocker classification). The dosage of cortisone and ACTH was held throughout the study at levels which produced suboptimal relief of symptoms in order to reduce complications. The hyperadrenal state was terminated in five patients because of a remission and in 27 patients because of untoward events. In the latter group were eleven deaths, and follow-up of twelve of the rest 2 to 3 years after discontinuation of hyperadrenalism revealed that eleven remained confined to a bed or chair. At the close of the study 36 patients remained on cortisone or ACTH. This group continued to manifest physical signs and laboratory evidences of rheumatoid activity, and in 21, progressive destruction of joints during hyperadrenal therapy was demonstrated by serial *x* rays. Attempts to terminate hyperadrenal treatment in this group have not been successful because of prompt rebounds, but ACTH and cortisone have continued to produce moderate or marked symptomatic relief in the majority.

Discussion.—DR. JOSEPH J. BUNIM (*Bethesda, Md.*): It is clear that patients who have mild rheumatoid arthritis and have done well on conservative measures should not be given steroid therapy, but how about those who have very severe rheumatoid arthritis? When a patient's disease is progressing rapidly and seems to show no signs of tapering off, that, in itself, seems to me the best indication for the institution of steroid therapy.

DR. HOWELL: In general, we agree on this point, but our experience suggests that if those patients who are progressing rapidly have associated inflammatory disease such as chronic pyelonephritis or bronchiectasis, the chance of salvaging them is very poor.

DR. EDWARD F. HARTUNG (*New York City*): Was the presence of amyloid degeneration determined in these chronic, well-established cases that did poorly, and is amyloid degeneration a factor in the poor results and the deaths?

DR. HOWELL: Two patients showed amyloidosis at autopsy which may well have contributed to their downhill course; in one of them amyloidosis was diagnosed several years before death.

DR. JEROME SIMSON (*Forest Hills, N.Y.*): How was the *x*-ray improvement manifested?

DR. HOWELL: Three of the five showed *x*-ray improvement; in two of these, it was merely a reduction of osteoporosis, in the third there was actual healing of punched-out bone lesions.

Heart in Rheumatoid Arthritis: A Clinical-Pathologic Correlation of 43 Autopsied Patients. By M. H. LEVIN, L. KAPLAN, S. MARCUS, H. J. WEINBERGER, and J. PATTERSON, JR., *Los Angeles, Calif.*

In an attempt to establish the clinical and pathological cardiac manifestations of rheumatoid arthritis, 43 autopsied cases were studied. The pathological findings were as follows:

Granulomatous lesions resembling subcutaneous rheumatoid nodules	10
Obliterative lesions of the pericardium	12
Nodular thickening of one or more valves	25
Inflammatory lesions of the ascending aorta	7
Amyloid infiltration	7
Arteritis of the coronary vessels	7
Arteriosclerotic heart disease	15
Cor pulmonale	7
Non-specific myocarditis	2
Granulomatous pericarditis	2

The pathological changes were correlated: age, sex, duration and classification of arthritis, presence of subcutaneous rheumatoid nodules, steroid therapy, psoriasis, iritis, clinical cardiac findings, congestive heart failure, response to therapy for congestive failure, electrocardiographic alterations, cardiac roentgenograms, other major diagnoses, and cause of death.

Clinically, arteriosclerotic heart disease was not distinguishable from the inflammatory alterations encountered in the hearts of these patients with rheumatoid arthritis, with the sole exception that in the presence of congestive heart failure the response to therapy of the two groups was usually good and usually poor respectively. Nonetheless, these data further substantiate the concept of rheumatoid heart disease as a multiphasic entity with many pathological manifestations. The observations seem to indicate that a given patient with rheumatoid arthritis, even an older individual, has a greater likelihood of having rheumatoid heart disease than arteriosclerotic heart disease.

Discussion.—DR. WILLIAM S. CLARK (*Cleveland, Ohio*): Dr. Levin has provided more evidence that there is a rheumatoid form of heart disease. Data so far accumulated indicate that three types of inflammatory lesions occur in the heart in rheumatoid arthritis:

(*a*) unquestionably rheumatic in nature,
(*b*) seeming to be rheumatoid in origin,
(*c*) unclassified.

I think we are reasonably sure that the nodule represents a form of rheumatoid heart disease, as does the aortitis which Dr. Levin demonstrated.

He observed a high incidence of nodules in these hearts, but it seemed to me that about half of his patients were nodule formers, and that may explain the higher incidence in this series of cases.

DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): It certainly has been interesting to watch developments in the past 14 or 15 years since Dr. Vogenoff and I presented a paper here before this society; papers from different parts of the world report quite different findings in this matter of the heart in rheumatoid arthritis.

It is reported by Egelius, Göhle, Jonsson, and Walgren* from Stockholm that they found little or nothing excepting perhaps a little pericarditis in an autopsy series. They concluded that there must be something wrong with the work that others, including Dr. Vogenoff and I, had done in finding these rather extensive cardiac lesions.

The subject does not seem to be settled even to-day, although the paper we have just heard supports those who find rheumatoid arthritis to be associated with cardiac damage.

In the past it was of academic interest to find that there were lesions in the heart, because clinicians said that as rheumatoid arthritis patients do not have much heart trouble we should just take note of it and not worry too much about it. But in the future, this may not be the case. For example, difficulties are resulting from the discovery of a remedy which frees the movements of rheumatoid arthritics, because osteoporosis leads to fractures; these cardiac lesions may also become more important as bedridden patients are able to get up.

Were any of these autopsied patients observed in recent years after having hormone treatment, and did it make any difference?

DR. LEVIN: These patients were autopsied consecutively from 1947 to the present time, and I have four additional cases which were autopsied very recently. Every patient with rheumatoid arthritis who has died in our institution has come to autopsy.

The data on the administration of steroid therapy was interesting. Approximately ten of these patients were on steroids and in several we found changes of the variety described. When the incidence of the various types of changes encountered in the group who received steroids was correlated statistically with the remainder of the group, no significant difference was noted.

DR. CURRIER MCEWEN (*New York City*): Since lupus raises its ugly head in so many of these diseases, was it explored in these particular patients?

DR. LEVIN: Diagnostic lupus cell preparations were not done in most of them, but no evidence of lupus was seen in the kidneys.

DR. DONALD GRAHAM (*Toronto, Ont.*): Did Dr. Levin find any lesions in the ascending aorta in patients who did not have spondylitis?

DR. LEVIN: Yes. Of the eight patients with aortitis, four had had peripheral arthritis only. Of the other

* *Annals of the Rheumatic Diseases* (1955), **14**, 11.

four cases, three had combined peripheral and spinal arthritis, and one had pure spondylitis.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): Of the 43 patients who were autopsied, 25 showed a nodular valvulitis in one or more valves; and 27 showed clinical evidence of cardiac abnormalities. I wonder what the physical examination of the patients now living in the same hospital would reveal.

In this particular group the sex ratio was much higher than in any ordinary group, since 97 per cent. were males, and that might account for some of the difference.

DR. LEVIN: We are aware of the difficulty in drawing conclusions from data on autopsied series. Dr. Mainland's work, pointing out the dangers encountered in trying to draw conclusions on the basis of autopsied material, is well known to us.

We do know our data are weighted because these patients were all veterans; they were primarily males with severely advanced rheumatoid disease, they had all been in the institution for a long time, and they all died. There are also probably other unknown factors.

We find a much lower incidence of detectable heart disease in living patients with rheumatoid arthritis, and this parallels the clinical findings described in recent publications, about 15 to 20 per cent.

DR. H. A. SMYTHE (*Toronto, Ont.*): I wonder if any important differences were noted between rheumatoid arthritis and spondylitis with regard to the heart lesions. In the large clinical series in Sunnybrook Veterans Hospital at Toronto, there are two important differences between the two groups: In the spondylitics there is a much higher incidence of lone aortic regurgitation, and a much higher incidence of long PR intervals or second degree heart block.

DR. LEVIN: We analysed the data from that point of view and found no difference between people with spondylitis and those with peripheral involvement. As far as the electrocardiograms were concerned, we found all kinds of varieties of E.C.G. abnormalities. Heart block was more common in the small number of patients who had uncomplicated arteriosclerotic heart disease than in those with rheumatoid heart lesions.

Nodular Vasculitis: A Manifestation of Systemic Rheumatic Disease. By PAUL J. VIGNOS, JR., J. LOWELL ORBISON, and WILLIAM S. CLARK, *Cleveland, Ohio.*

Nodular vasculitis has been described by Montgomery and others (1945)* as a localized skin disease characterized by chronic nodular lesions of the lower legs. Three patients will be discussed in whom the local nodular vascular lesions were associated with systemic involvement, suggesting that they may be manifestations of generalized rheumatic disease.

The nodose lesions occurring on the lower legs, for periods of 3 to 16 years, were painful, chronic, recurrent, and non-ulcerative. Systemic manifestations in all three included non-deforming, chronic arthritis which was a major complaint and antedated the nodules. Other systemic manifestations were myositis, hypertension, episcleritis, migraine headaches, and abdominal haemorrhage. Differential sheep cell agglutination tests were negative. "L.E." cells were present in one.

* *J. Amer. med. Ass.* (1945), **128**, 335.

Histopathological studies of the skin revealed inflammation and necrosis of arteries and veins deep in the dermis and in the subcutaneous fat. All patients had lesions characterized by necrosis of the vessel walls accompanied by acute inflammation. In addition to this acute lesion, two patients had scarred and distorted vascular walls and a large lumen filled with connective tissue; these sites of previous injury were unusual in that recent coagulative necrosis had been superimposed on the old injury and had partially destroyed the connective tissue in the lumen and also the vessel wall. Apparently the lesions not only tend to recur, but to recur at sites of previous lesions.

Discussion.—DR. THEODORE B. BAYLES (*Boston, Mass.*): With Dr. Edward Edwards at the Peter Bent Brigham Hospital and Robert Breck Brigham Hospital, we have been interested in these vascular lesions for the last 2 or 3 years. Am I right in thinking that the patients described had classical rheumatoid arthritis?

We have observed haemorrhage into the subcutaneous tissue, and I should like to know whether this was observed by you? We think that this primarily involves the vein, although you mentioned arterial involvement.

Our patients mostly had this lesion on the dorsum of the foot, and I wonder where the lesions were located in your patients.

DR. VIGNOS: The arthritis exhibited by our patients was not typically rheumatoid in nature. Joint complaints had been present for many years with episodes of synovitis in all, but none had deforming arthritis.

We have seen no skin haemorrhages, nor other lesions of the haemorrhagic or necrotic type such as are frequently seen in lupus erythematosus or periarteritis nodosa. There were no skin lesions except the nodules, and we feel that this was an unusual feature in view of the high incidence of varied skin lesions in lupus erythematosus and periarteritis. There was involvement of both arteries and veins in these patients.

These lesions frequently appeared on the anterior aspect of the lower leg at the pre-tibial level. They appeared posteriorly in the soft tissue overlying the gastrocnemius muscle, and also in the ankle region, near the malleoli. We have seen only a few lesions over the dorsum of the foot, which was one of the less frequently involved sites.

DR. J. P. HAMILTON (*Memphis, Tenn.*): Was there a history of allergy in any of these patients?

DR. VIGNOS: We did not elicit a history of allergy in any of them; there has been no asthma nor other manifestation that might be listed under that heading.

Behaviour of the Agglutination Activating Factor of Rheumatoid Arthritis with Immune Precipitates. By JOHN H. VAUGHAN, *Richmond, Va.*

The agglutination activating factor (AAF) of the sera of individuals with rheumatoid arthritis (Rose, Ragan, Pearce, and Lipman, 1948) is capable of interacting with several types of cells sensitized with antibody of various animal species (Pike, Sulkin, and Coggeshall, 1949; Wager, 1950). This apparent lack of immunological specificity of AAF has suggested that its behaviour may be more like that of serum complement than that of serum antibody and that it might be profitably studied with immune precipitates.

Washed immune precipitates from antisera of rabbits immunized with recrystallized egg albumin (Ea) or conalbumin (Ca) were added to heat-inactivated rheumatoid and normal human sera. Increasing quantities of Ea-anti Ea absorbed increasing amounts of nitrogen from the rheumatoid arthritis sera. No nitrogen was absorbed from individual or pooled normal sera. With the absorption of increasing quantities of nitrogen from the rheumatoid arthritis sera, the AAF activity of the supernatant was first reduced and then abolished completely. In control studies, powdered asbestos, filter paper, and barium sulphate did not absorb any measurable nitrogen nor reduce the AAF titre. Ca-anti Ca precipitates behaved similarly to Ea-anti Ea precipitates.

The interaction of AAF with immune precipitates appeared to be an equilibrium reaction. Whereas a plateau of absorbed nitrogen was reached by the addition of increasing quantities of Ea-anti Ea to given volumes of rheumatoid arthritis sera, new Ea-anti Ea added to the supernatants at the plateau level absorbed some additional nitrogen. The total amount of nitrogen absorbable from high-titre rheumatoid arthritis sera was 100-200 μg. N/ml., a value corresponding to about 1-2 per cent. of the total protein of the sera.

The use of immune precipitates for the study of AAF offers a promising tool for the further development of our understanding of the nature of this factor.

Discussion.—DR. MORRIS ZIFF (*New York City*): Dr. Vaughan's work seems to me to be of great importance. For the first time the sensitized sheep cell agglutination reaction, which has hitherto been based on an indicator system which could not possibly play a role in human disease, has now been related by Dr. Vaughan to the type of immune system which might play a role.

DR. RALPH H. BOOTS (*New York City*): Despite the many reports yesterday of investigations of adrenal cortical hormones, it is still highly questionable whether the secrets of rheumatoid arthritis will be answered by this approach, and it is refreshing to have a paper such as Dr. Vaughan has given this morning which has nothing to do with steroid hormones.

The younger research workers in this society should be encouraged to try other types of attack on this disease and I wish to congratulate Dr. Vaughan on continuing his work with the immunological approach.

Natural History of Marie-Strümpell Arthritis (Rheumatoid Spondylitis). By BARUCH S. BLUMBERG, *New York, N.Y.*

During the past 28 years, the diagnosis of Marie-Strumpell arthritis, or rheumatoid spondylitis, has been made on approximately 300 patients at the Presbyterian Hospital. We have been able to contact more than 50 per cent. of these patients and personally interview, examine, and perform blood tests and *x* rays on over one hundred of them.

There is a follow-up of 20 years or more in many of these patients and in most cases, *x*-ray and laboratory confirmation of the clinical findings are available. On the basis of these data, we have reached some conclusions concerning the natural history of this disease.

The material has been co-ordinated by plotting certain objective and subjective data as a function of the duration of the disease. This suggests that, in the typical case, the progression of the objective *x*-ray findings is relentless, while the functional disability and pain are by no means so, and may, indeed, appear to improve. The data also suggest that there is a period of rapid progression of *x*-ray and physical findings early in the disease. These objective changes then reach a plateau at which the patient appears to adjust and then to carry on his activity with remarkably little functional disability. The final bony involvement is variable and only a few go on to marked deformity. This should be appreciated in evaluating the necessity for radical therapy in the early stages of the disease.

Many of the patients have had symptoms of peripheral arthritis, but only a few subsequently developed objective changes in the peripheral joints. It is the latter group which seems to do less well.

Persons with rheumatoid spondylitis appear to be very effective. They are for the most part married and have children. They are nearly all working and maintaining themselves even in the face of apparently overwhelming skeletal deformity.

Discussion.—DR. IVAN F. DUFF (*Ann Arbor, Mich.*): The details of the extent of involvement of the spine or sacro-iliac joints at the time of initial examination is of particular interest to us. In 1940 Dr. Charlie Smyth and Dr. Richard Freyberg reported to this group the effect of *x*-ray therapy on selected patients with rheumatoid spondylitis. Dr. W. D. Robinson made a second report in 1947. A third follow-up study was conducted by the Rackham Arthritis Research Unit, with particular reference to the effect of *x*-ray therapy in fifty patients who at the initial examination, 7 to 16 years ago, had no *x*-ray evidence of involvement of the sacro-iliac joints (5), changes limited only to the sacro-iliac area (31), or changes limited to the sacro-iliac joints and lumbar spine (14). This work was made possible by the efforts of Dr. Keith Averill who carried it out while holding a vacation fellowship as a senior medical student.

In our series there was no control group of patients with spondylitis not treated with *x*-ray therapy. For this reason we have listened closely as Dr. Blumberg has described the natural history of the disease. It is of interest that our experience is quite similar to that reported by him. In this group 82 per cent. did well symptomatically, and 60 per cent. pursued a favourable objective course, but in approximately 40 per cent. there was relentless progression of the disease as demonstrated by the *x*-ray changes throughout the spine and neck.

In our experience there appears to be some relation between the benefit of *x*-ray therapy and the duration of the disease. Those who had had spondylitis for less than 2 years did better symptomatically and objectively than those who had had it for a longer period. This point is of significance perhaps in relation to early diagnosis.

Peripheral joint involvement, which in our experience may antedate the back symptoms, occurred at some time in almost 50 per cent. At the end of our study, however, objective manifestation of active peripheral involvement was not frequent. Indeed, only one patient at the last follow-up was taking steroids to control symptoms related to peripheral involvement. Peripheral joint involvement in spondylitis does not necessarily behave as one might expect from one's experience of

rheumatoid arthritis without spondylitis. In spondylitis it is apt to pursue an indolent course, and some of the patients who become free of back complaints do very well despite obviously swollen joints. In a few patients with active involvement in the back, improvement in the peripheral synovitis, particularly of the knees, appeared coincident with improvement related to *x*-ray therapy.

In our group, girdle-joint involvement appears to have developed late in the course of the disease. Manifestations of girdle-joint involvement developed in at least 50 per cent.; in approximately 16 per cent. hip involvement had become a major disabling problem. Eye disease was also important, since iritis or similar involvement was observed at some time in fourteen of the fifty.

We agree with Dr. Blumberg that, by and large, as representatives of the rheumatic diseases, the patients with rheumatoid spondylitis often appear to be superior individuals. They frequently make a good adjustment to their disease and its limitations, and are productive citizens in spite of it. This is not to deny, however, that spondylitis, particularly when accompanied by bizarre skeletal deformity, as of the cervical spine, or by blindness, can be a frightful disease.

DR. BLUMBERG: All the patients we evaluated had involvement of the sacro-iliac confirmed by *x* ray. This group was perhaps somewhat more severely involved than one would find in a private practice.

Some of our patients had received *x*-ray therapy and some not, but the two groups were not randomly selected and are therefore not comparable, though we found that those who did not receive radiotherapy had somewhat more physical deformity than those who did.

DR. CORNELIUS H. TRAEGER (*New York City*): In this remarkable group of patients and wonderful follow-up which Dr. Blumberg had, there are two aspects which were not commented on and I wonder if Dr. Blumberg had made these observations. First, in the large majority of patients who were able to continue work, was it ever necessary for them to change their occupation during the development of the disease?

And secondly, were there any familial tendencies or hereditary factors observed in this group?

DR. BLUMBERG: Some of them did change their occupation, but most of them work for remarkably long times at responsible and physically difficult jobs. We had one woman who, after having been seen in our hospital, went home and spent the next 10 or 15 years picking cotton. I think, as a rule, they maintain their jobs fairly well, although we did not study the occupational history in great detail. We were satisfied to determine their gross functional status.

There was a definite familial incidence. We had two families in which there were more than two members involved, in one case two brothers and a sister, and in a second the patient, his father, grandfather, and great grandfather.

DR. PAUL H. CURTISS (*Cleveland, Ohio*): Was any note taken of any surgical procedures such as orthoplasty, and did it have any effect on change in classification or course?

DR. BLUMBERG: There were two patients who had osteotomies of the spine in this group and they were doing well, with a good cosmetic result. However, it is difficult to determine whether they would have done well had they not had the operation, as many of those who were not treated surgically also did well.

DR. JOHN G. KUHNS (*Boston, Mass.*): I dislike injecting a pessimistic note into this very interesting study. We followed some four hundred cases of spondylitis for from 5 to 14 years and our functional results are inferior to those Dr. Blumberg has mentioned; 35 per cent. had ankylosis of the hips, 30 per cent. had peripheral joint involvement, at least 10 per cent. had iritis with blindness or some damage to the eyes before the advent of hormone therapy, and at least 20 per cent. had operations for various gastric difficulties.

DR. BLUMBERG: What was their functional ability?

DR. KUHNS: Only about 50 per cent. of them could be considered in Group I.

DR. BLUMBERG: A good number of our patients had peripheral joint involvement, but a digression might be made on this point. Some 60 per cent. of the patients gave a history of peripheral joint involvement. However, only half of that number, about 30 per cent. of the total, actually showed objective changes of joint involvement when we saw them.

Of those who had the peripheral joint involvement, it was practically all in the hips and knees and perhaps to a somewhat lesser extent the shoulders. The involvement of the wrist and fingers, so characteristic of typical peripheral rheumatoid arthritis, was extremely rare in the group that we saw. There were only four or five out of perhaps one hundred who had evidence of objective wrist and finger involvement.

The difference in selection of the groups, among other things, could account for our different results.

Pathways of Urate Synthesis in Gout. By JAMES B. WYNGAARDEN and ALBERTA BLAIR,* *Bethesda, Md.* (introduced by J. J. Bunim). Read by Dr. S. Segal.

The present study was designed to compare rates and extents of glycine incorporation into purines of normal and gouty persons, to gain information about the biosynthetic intermediates of normal and abnormal urate production. One control (osteo-arthritic) and two gouty men were given 5 μc. glycine-1-C^{14} (0·13 mg.) orally while on a purine-free, low-protein diet. Urinary purines were isolated as copper salts and dissolved in HCl, and uric acid separated by reduction of volume and chilling. Residual purines were further purified *via* copper and ammoniacal silver precipitations, and placed on Dowex-50-H^+ column (200-400 M, 2·5 × 12 cm. bed) as hydrochlorides. Separation was achieved by gradient elution with HCl (0·15→2·65 N). Purines were recovered, recrystallized, and counted.

In the control, urate specific activity reached a maximum of 350 c.p.m./mM on the third day. Hypoxanthine specific activity was greater than urate on Day 1, and fell rapidly to low values by Day 3. Adenine values, however, were maximal on Day 3, and declined in parallel with urate, but at values approximately half those of urate. Xanthine values were about 90 c.p.m./mM throughout the study, suggesting appreciable dilution of labelled xanthine by xanthine derived from metabolically less active sites. The hypoxanthine data suggest a rapid pathway for urate synthesis in the normal, possibly *via* inosinic acid; the adenine data suggest a second slower

* National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U.S. Department of Health, Education, and Welfare, Bethesda, Md.

pathway, quantitatively the more important, possibly involving nucleic acids. One gouty subject who excreted normal quantities of urate showed a strikingly abnormal pattern of glycine incorporation. Urate specific activity was 910 c.p.m./mM on Day 1, followed by a precipitous decline. A second gouty subject who excreted excessive quantities of urate (1,135 mg./day) also showed an exaggerated rate and extent of glycine incorporation into urate. In this subject hypoxanthine enrichment was maximal on Day 1 and thereafter declined slowly. Hypoxanthine values were at all times less than those of urate. These results suggested that the "inosinic acid pathway" was involved in both rapid and excessive urate synthesis in this subject, but also suggested the possibility of an accessory pathway for urate synthesis, not involving the usual intermediates, responsible for a part of the over incorporation of glycine into urate.

Clinical Course of Acute Gouty Arthritis treated with Oral Phenylbutazone: Relationship of Drug Dosage Schedule and Serum Drug Level. By GEORGE M. WILSON, JR., ELSTON R. HUFFMAN, and CHARLEY J. SMYTH, *Denver, Col.*

The control of the manifestations of acute gouty arthritis by phenylbutazone has now been well established. However, the characteristic pattern of the response of gout to the drug, and the rapidity of response as related to the drug dosage schedule and effective serum levels, have not been sufficiently emphasized.

Sixty consecutive attacks of acute gouty arthritis, occurring in 42 males, were treated with various dosage schedules of oral phenylbutazone. A similar pattern of response to the drug was observed in all cases. This was characterized by two phases. Initially, a marked subjective (50-100 per cent.) relief of joint pain occurred without significant objective changes in the other signs of joint inflammation. 24 hours or more later, complete resolution of all evidences of joint inflammation occurred. In 56 attacks (89 per cent.), subjective pain relief occurred within 24 hours. In 49 attacks (73 per cent.) complete resolution of all findings of inflammation occurred within 72 hours.

The promptness with which the two phases of the response occur, varied with the dosage schedule of phenylbutazone. When a 400 or 800 mg. stat dose was given, relief of pain occurred within 4 hours in 16 of 19 attacks occurring in 19 patients. Complete resolution within 24 hours occurred in 8, and within 24 to 72 hours in 15. When 100 mg. every 4 hours (400 mg./day) was given, pain relief occurred within 4 hours in only two of 22 attacks occurring in sixteen patients; sixteen attacks were relieved in from 4 to 12 hours. Complete resolution within 24 hours occurred in fourteen attacks, and in from 24 to 72 hours in seven. When 200 mg. every 4 hours (800 to 1,200 mg./day) was given, pain relief occurred within 4 hours in only one of fifteen attacks in eight patients. Thirteen attacks were relieved in from 4 to 12 hours after drug ingestion. Resolution within 24 hours occurred in six attacks, and in from 24 to 72 hours in seven.

These observations indicate that the pain of acute gout is most promptly relieved by a 400 or 800 mg. stat dose of phenylbutazone. Complete resolution of the attack occurs earliest with an intermittent dosage schedule. It is recommended, therefore, that acute gout be treated with 400 mg. stat of phenylbutazone, followed by 100 mg. every 4 hours until all evidence of acute joint inflammation resolves. This, in our experience, rarely requires more than 4 days and no evidence of toxicity has been observed.

Observation in 11 cases of the serum phenylbutazone level, at the time when significant relief of joint pain occurred, will be presented. These serum phenylbutazone levels ranged from 2·1 to 3·9 mg. per cent. regardless of the dosage schedule. These levels are insufficient to cause uricosuria.

Renal and Anti-Inflammatory Effects of Phenylbutazone Metabolites and Derivatives in Gouty Subjects. By T. F. YÜ, B. C. PATON, J. J. BURNS, J. M. STEELE, B. B. BRODIE, and A. B. GUTMAN, *New York, N.Y.*

New phenylbutazone derivatives are being synthesized in an attempt to develop a drug retaining the anti-inflammatory and uricosuric properties of phenylbutazone, but with fewer undesirable effects. After preliminary screening, five of these compounds were studied. The anti-inflammatory effects were observed in acute gouty arthritis (25 cases), and simultaneous renal clearances were measured in interval gout (33 cases).

None of these compounds substantially alter the inulin clearance, all depress PAH clearance.

G-25671, the phenylthioethyl analogue of phenylbutazone, may be useful clinically; it has moderate anti-inflammatory activity and a very marked uricosuric effect, with minimal sodium and water retention.

G-25903, the phenylthiopropyl analogue, has little anti-inflammatory effect and only mild uricosuric action.

G-13838, the isopropyl analogue, causes transient uricosuria and marked sodium retention, and has no anti-inflammatory effect.

Two of the compounds are metabolites recovered from the urine of patients receiving phenylbutazone.

G-28231, the β-hydroxybutyl derivative, is not anti-rheumatic but has marked uricosuric and very little sodium-retaining effects.

G-27202, the p-hydroxyphenyl derivative, has the potent anti-rheumatic activity of the parent compound and a rather mild uricosuric effect, and causes rapid and marked sodium retention.

The studies demonstrate that the anti-inflammatory, uricosuric, and sodium retention effects of phenylbutazone can be dissociated by appropriate alterations in molecular structure.

Discussion.—DR. L. MAXWELL LOCKIE (*Buffalo, N.Y.*): Has Dr. Huffman had the opportunity of studying similar cases in which colchicine was administered at the same time as the phenylbutazone? It was our impression at Buffalo that if colchicine were given in small doses such as 0·5 mg. with a 200-mg. dose of phenylbutazone every 2 hours for three or four doses, that the response was very prompt and lasting.

DR. HUFFMAN: We have made no attempt at comparing colchicine with this substance.

DR. ARTHUR I. SNYDER (*New York City*): Has Dr. Huffman given any consideration to the duration of attack before beginning direct therapy, and to the therapeutic response at various dose levels?

DR. HUFFMAN: A number of the attacks had gone on for 5 to 6 days before we started therapy. The Butazolidin was then effective in those instances, but perhaps the response was slower.

DR. JOHN BURNS (*New York City*): It was pointed out that phenylbutazone had both a phenolic compound and an alcohol derivative. We are interested in the phenolic compound because here we have one which is metabolized by the introduction of a phenolic group into phenylbutazone which stays in the body as long or possibly longer than Butazolidin. In fact, we are able to detect considerable concentrations of the compound in the plasma level of about 30 mg. per litre of metabolic concentration, where Butazolidin occurs at about 100 mg. per litre. At present we are working to see whether this particular compound could mediate part of the action of the phenylbutazone itself in anti-inflammatory effect and sodium exclusion.

DR. J. NORRIE SWANSON (*Toronto, Ont.*): Were any toxic effects of Butazolidin encountered during the short-term therapy employed, and were there any patients whose attacks of gout did not respond to Butazolidin?

In Toronto, we have a series of gouty patients comparable in number to Dr. Wilson's. Four patients did not respond to Butazolidin after receiving 600 mg. daily for 4 days, but then responded rapidly to intravenous colchicine, some relief of pain being noted as early as half an hour after injection. One injection of 3 mg. colchicine intravenously is frequently, in our opinion, of greater and more rapid benefit, without nausea or vomiting, than 1 oral dose of 600 mg. Butazolidin.

DR. HUFFMAN: We have had no failures, though we are aware that others have, and we have had no serious toxic effects. We have given doses of 800 mg. to eighteen patients, some for the purpose of obtaining serum levels and others for therapeutic reasons. Approximately six of these patients noted a little stomach distress after receiving the single large dose, but in no other instance have we had toxic effects that could be ascribed to the drug. One patient vomited his 400-mg. dose, but later that day was discovered to have an intestinal obstruction for which he was intubated, and later on, he was able to tolerate the same dosage very nicely.

DR. YÜ: In carrying out the previous studies, we encountered skin rashes in two cases after G-26571. One of the two subjects had a similar hypersensitivity to phenylbutazone.

DR. J. J. BUNIM: Will Dr. Yü tell us how she evaluates any kind of inflammatory effects?

DR. YÜ: The anti-inflammatory effects were evaluated in patients with acute gouty arthritis. All the observations were made by the same person. I usually recorded the degree of inflammation the day before I started the treatment, noting the degree of swelling, redness, heat, limitation of motion, and tenderness. Then I gave the medication, and after 24 hours examined the patients again for signs of inflammation. Complete response obtained in from 24 to less than 48 hours was considered good. Any response which took place only after 48 to 72 hours was considered fair. If they still had some sign of inflammation after 72 hours I considered the response to be poor. Any that do not respond after 96 hours, I considered as entirely negative.

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PANEL DISCUSSION

(MODERATOR: DR. ALBERT J. KEY)

Reconstructive Surgery in Arthritis

Prevention and Control of Arthritic Deformities in the Hand. By JAMES E. BATEMAN, *Toronto, Ont.* (By invitation.)

In the rehabilitation of the upper extremity, emphasis should be placed on the function of the hand. The management of the deformities resulting from arthritis requires prevention as well as correction, and the two are complementary.

Splinting is the most effective measure in preventing deformity and constitutes a real challenge in the rheumatoid hand. To be useful to arthritics a splint must be simple and flexible. It must control the deformity yet not produce pain nor irritate sensitive parts. It should be light, easily moulded, yet durable. These requirements have been met by the development of a new splint which has worked most effectively. The apparatus consists of a forearm and wrist chassis to which the finger controls are added. Individual springs regulate the fingers while deformity of the hand as a whole is controlled by a master spring. The corrective parts are kept on the dorsal surface so that the palm is free. In this fashion use of the hand as a whole can be encouraged. The splint is made to measure and so constructed that it may be worn for years if necessary.

Established deformities requiring surgical correction arise in all forms of arthritis, but chiefly in post-traumatic and rheumatoid lesions. In the wrist the most effective procedure to correct deformity and prevent pain is arthrodesis. It is recommended that fixation extend from the radius to the base of the metacarpal so that all deforming factors are controlled. A modified Brittan type of arthrodesis has proved most satisfactory.

Deformity in the fingers is a difficult problem for many reasons. Only limited use may be made of arthrodesis because of the infinite demand for varied positions of the digits. Efforts, therefore, should be toward some form of arthroplasty. In a non-weight bearing joint the possibility of replacement arthroplasty is most attractive. To this end a vitallium prosthesis has been used in interphalangeal arthroplasty. The technique is to resect the damaged joint surface, usually the proximal segment, and to replace the whole tip of the phalanx. This results in a stable joint, but leaves a considerable degree of controlled movement without pain.

Discussion.—DR. J. NORRIE SWANSON (*Toronto, Ont.*): If one considers in a little more detail, how the deformity arises, one may arrive at a different conception of splinting. I believe the most important factor in the production

of deformity is muscle spasm. As has been shown by Kellgren of Manchester, England, and Gardner of Detroit, as soon as there is pain in a joint, the adjacent muscles are thrown into spasm to prevent movement. Although the spasm is protective to the joint, it is eventually destructive to the muscle itself. It follows, therefore, that one of the first things to be dealt with in the prevention of deformity, is to *relieve* the spasm. Anything, however, that *increases* the spasm is, I think, wrong: I do not believe that to put the fingers in a spring splint as Dr. Bateman suggests, is resting them. That is increasing the tension, and so will increase the spasm, thereby aggravating the pain, and perhaps even making the arthritis worse. It is not the right thing to do in the active stage of the disease.

Later, when the disease activity has decreased and it is soft tissue contracture that is responsible for the deformity, it may be right to use this type of splinting. But until then, the hands should be rested comfortably in the usual plaster of paris, or another type of plastic splint, so that the pain is relieved. The spasm will nearly always then disappear. This is a quicker, more comfortable, and more physiological way of relieving spasm, or of preventing or treating early deformity.

Then, again, I do not think it is very easy to wear a splint with springs during the night. However, I do not wish to detract from the usefulness of Dr. Bateman's paper as a whole.

DR. BATEMAN: Dr. Swanson's observations are very pertinent. Certainly the initial disturbance is one of spasm, but I have never been able to assess and decide when that spasm passes into the deforming stage of shortening. Electromyelographical studies show disturbed electrical potentials indicating spasm, but after a while that spasm goes, and the muscle is shortened, though it looks the same on the outside. I was speaking primarily of correcting the later well-established deformities, but if we could decide when the so-called spasm becomes shortening, we should be able to control these deformities much better.

DR. CURRIER MCEWEN (*New York City*): Could Dr. Bateman enlarge on the role of exercises, and also on arthroplasty without prosthesis in the correction of deformities of the hand?

DR. BATEMAN: Exercises, voluntary movements, have a place in the whole programme. A hand will be encouraged to exercise if it is kept in the position of function and free of obstructive apparatus. It is difficult to encourage the use of a hand that splinted by something that blocks the normal grasping tendency.

Once the deformity is reasonably well controlled, I think that exercises can be used perhaps without the splint, but the spring splint in itself is an exercise apparatus. The coil spring at the base produces an obstruction and helps to control flexion so that the flexures can work against it.

On the question of arthroplasty apart from replacement arthroplasty, many early contributions on arthroplasty, particularly in rheumatoid arthritis have been made. The principle of replacing the damaged area is most attractive because it allows us to correct the deformity completely and then we start off with a good joint surface to initiate movement.

As a general principle, particularly in rheumatoid arthritis, arthroplasty is not yet sufficiently well developed to be considered.

DR. DONALD F. HILL (*Tucson, Ariz.*): How many patients have worn these splints, and for how long? Have you evaluated them after prolonged use?

DR. BATEMAN: We have applied these splints in between 75 and 100 patients, and some have worn them for 3 or 4 years. We have no well-organized follow-up on the exact degree of deformity corrected, but the important thing is that these patients are sufficiently improved from the start to become used to their splints and to be content to use them for a long time. Some patients have even gone back to work using their splints.

MODERATOR KEY: Do they sleep in them, too?

DR. BATEMAN: Yes.

DR. ROBERT S. HORMELL (*Boston, Mass.*): We, too, have used spring and rubber elastic splints in the treatment of rheumatoid deformities, but without much success. Under our best directions the deformities progress relentlessly while the patient is using the splints and doing his exercises. Perhaps our splints have not been used long enough or often enough because of discomfort or difficulty in their application. We suspect, however, that the reason for continued progression while under treatment is that adaptive changes in the epiphyseal portions of the bones progress, even in the absence of activity of the rheumatoid process. We feel that these adaptive changes are the response of the bone to the static and kinetic forces of gravity and of muscular pull on the bones and joints.

Dr. Bateman's splint includes a snap fastener device, which is very neat and very necessary. Buckles and other fasteners are not so suitable as this simple fastener, which the crippled rheumatoid can remove with ease. Where can this snap fastener be obtained?

DR. BATEMAN: I do not think elastic traction is good enough in correcting these deformities. It is not steady enough, you cannot adjust it to the exact degree which is required, and as the deformity improves, you cannot continue to correct it.

The most serious deformities of severe atrophic arthritis, telescoping of the fingers, and so on, may be prevented if the initial lesion is treated properly. If the metacarpal phalangeal joint is kept as close to the mid position as possible, the interossei are not able to shorten and so produce the severe telescoping.

These splints have been made in our limb factory at the Department of Veterans Affairs in Toronto, and also by brace makers in the city.

DR. ABRAHAM S. GORDON (*Brooklyn, N.Y.*): Is Dr. Bateman familiar with the splint for the ulnar deviation deformity that I described a number of years ago? This consists of a simple glove made out of tough but thin material—similar to that used for elastic stockings. The glove is made to measure from the middle of the forearm to, but not including, the terminal phalanges of the hand. At the thumb, which is not involved in the deformity, the glove is cut down to the base of the metacarpophalangeal joint. This permits the free use of all fingers while the glove is worn. For the entire length of the glove, half-inch wide tapes are sewn on the ulnar side and on the dorsal and ventral surfaces at the ring finger, and into these tapes are inserted thin steel bars, about $\frac{3}{8}$ in. wide. These are somewhat flexible, but firm enough to correct the deformity. Then a longitudinal cut is made on the ventral surface from the end of the glove at the middle of the forearm to a point about the centre of the palm, and a zipper is sewn into the opening. With the zipper open the glove is easily put on by the patient, and when it is closed the deformity is straightened.

This is a very simple type of splint and I have had quite a few of them made. The patients like it very much and they can sleep with the gloves on without any discomfort. The steel bars may be slipped out of the tapes for washing.

Reconstruction of the Knee in Rheumatoid Arthritis. By ROBERT L. PRESTON, *New York, N.Y.*

Inspection of disabled joints at operation reveals that the most characteristic features of the deforming pathology of rheumatoid arthritis are the soft tissue changes in and around the joints and in the muscles, fasciae, and skin. In most instances, the pathological changes in bone and cartilage do not cause disability.

Musculo-skeletal disability due to soft tissue pathology often can be prevented by protection of inflamed joints from trauma, prevention of deformities, and the restoration of strong and accurate muscular control by means of corrective exercises.

However, if fixed deformities are permitted to develop, the soft tissue pathology is still amenable to correction, but extensive reconstruction is usually required.

If function is to be restored to a severely disabled knee, an operation must be done which is extensive enough to correct all the principal features of the deforming pathology. The contracted tissues must be lengthened so that the knee can be brought into full passive extension. The intracapsular causes of impaired active and passive motion in the anterior compartment of the joint must be eliminated by excision of scar, removal of the irregularities of the articular surfaces, and restoration of adequate intracapsular space. Physiological tension must be restored to the overstretched extensor motor apparatus so that the scarred and atrophic extensor muscles can work at maximum advantage to move the joint into the weight-bearing position.

In all except the rare case in which the bony degeneration is so severe that a stable, painless joint will not result from any procedure except fusion, the objective of the operation is a knee which can be moved painlessly through at least the minimal range necessary for ambulation. This objective is achieved in many cases.

Discussion.—DR. MORTIMER ELKINS (*Hampton, Va.*): What are Dr. Preston's views on further attempts at rehabilitation of a contracted knee? We had two patients with rheumatoid arthritis with flexion contraction of the knees, and by using plaster casts we straightened the knees sufficiently for the patient to walk on metal bar splints.

What does he feel about the medical attempt to rehabilitate the knees?

DR. PRESTON: I don't like the use of wedged casts in these cases because if the scar tissue surrounding the joint is extensive and the contractors are firm, complete correction of the deformity cannot usually be accomplished and the disability almost invariably recurs.

Stretching by any means, either by wedged casts, traction, or under anaesthesia, should be limited to cases in which the contractures are slight and the adhesions fragile, in which the pathology is more severe than can be handled by corrective exercises.

Cutting the scar and the contracted tissues and cleaning up the joint in a surgical operation restores a greater degree of free motion, and this type of procedure is not so liable to be followed by post-operative recurrence.

DR. RICHARD A. FREYBERG (*New York City*): Dr. Preston has given an excellent exposition of the nature of the deformity and the practical means of correcting anatomical abnormalities. We who have to deal with these deformities fully appreciate that after the surgeon has made such successful reconstructions, a prolonged programme of functional rehabilitation is required.

Has Dr. Preston found systemic steroid therapy or local intra-articular hydrocortisone useful in either pre-treatment or post-treatment?

DR. PRESTON: We should like very much to instill local hydrocortisone at the time of surgery but we have never been able to figure out how to use it, because at the completion of the operation there are so many openings in the joint that it would leak out. As soon as we possibly can, we start both local and systemic hydrocortisone.

These steroids make it easier to rehabilitate these patients post-operatively. I know that there is some difference of opinion as to whether they actually cut down scar formation post-operatively, but from the practical standpoint, observing many of these cases, I feel that they must do so, because in the cases in which the steroids are used we have less trouble in securing the functional result and the entire situation is much more favourable.

DR. JOHN W. SIGLER (*Detroit, Mich.*): What procedure was employed in the first case Dr. Preston presented?

DR. PRESTON: In both cases the three-phase reconstruction operation was done. Phase 1 consists of posterior capsulotomy and lengthening of all the tissues on the flexor side of the joint; everything except the nerves and vessels. In Phase 2 the anterior aspect of the joint is opened for the correction of any pathology which will interfere with the active motion of the joint. In Phase 3 the slack is taken out of the extensor motor apparatus if it is too lax.

DR. CURRIER MCEWEN (*New York City*): The question of wedge casts was raised a few moments ago. I think wedging is a dangerous procedure; that if the correction cannot be achieved by less traumatic means than wedge casts—that is, by simple exercise and perhaps mild stretching under anaesthesia, followed by some traction—it is far better not to try to wedge but to move right on to an open operation.

In the patients whom I have had an opportunity to follow, it seems to me that every time we tried wedging, we got into a worse situation than we had before.

DR. DONALD F. HILL (*Tucson, Ariz.*): I heartily agree with the last statement, that mild procedure is fine; rather than use too much force, surgery will do a neater job with less trauma. We have seen much improvement in our knee operations in the last 5 years.

What did Dr. Preston do with the lower ends of the femur after reshaping it? Was fascia used as a lining?

DR. PRESTON: Only one element of the joint, the lower end of the left femur, was left covered with raw bone. Inasmuch as the opposing element, the tibia, was covered with scar, pannus, and some articular cartilage, it was not necessary to put in any membrane. Interposing a membrane is only required when two opposing surfaces will be raw.

DR. BERNARD M. NORCROSS (*Buffalo, N.Y.*): What dose do you use in the knee joint? It has been our experience that putting in doses of 250 and 300 mg. makes a significant difference and the effect lasts longer.

DR. PRESTON: We have not been using dosages higher than 75 to 100 mg.

DR. THEODORE A. POTTER (*Boston, Mass.*): The type of case that Dr. Preston has explained to-day is probably entirely different from the arthritic joints that we see in Boston. The type of joints we see have extensive intra-articular damage of bone and cartilage, and such procedures are only suitable to very few.

We call this the joint débridement and it works very well in the osteo-arthritic patient, but in our hands is most unfavourable in the rheumatoid arthritic. In a severely damaged joint, we have two procedures to choose from: fusion or arthroplasty.

In the very mild cases, serial applications of casts is sufficient to straighten out the knee joint, provided there is not intra-articular damage.

MODERATOR KEY: Is Dr. Paul Holbrook here? I learned something from him about 20 years ago about the knees. I have refrained from making remarks, but silence does not mean consent on my part to either of these papers.

Paul, you tell them about your excellent results with repeated manipulations under anaesthesia.

DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): Concerned at the endless bent knees of our long-term chronic patients with rheumatoid arthritis, we began studying the orthopaedist's methods, in trying to correct flexion contractures of the knee.

We felt, and still feel, that a straight knee is better than a bent knee. The earlier you can straighten the knee, the better it will be, regardless of the general activity of the disease. The longer the knee is bent, the more difficult it will be to straighten, and the more intra-articular damage will occur.

We did a large series of manipulative corrections under anaesthesia, sometimes not getting a complete straightening in one stretching and having to do it again, being as gentle as we could and yet bold enough to try to succeed in straightening the knee.

Out of more than 100 which we had done up to 10 or 15 years ago, about seventy or more are walking, and have maintained straight legs after manipulation.

This is not to say that bad knees ought not to have surgical intervention, and we now have enthusiastic and co-operative orthopaedists who help us a great deal with the bad knees. We still feel that we can readily and quickly straighten the easy ones early in the disease.

MODERATOR KEY: Dr. Preston, you have one question to answer about the difference between arthritis in Boston and New York.

DR. PRESTON: In certain cases there is too much intra-articular bony pathology to expect a painless, stable knee to result from any procedure except fusion. But, as the years pass, this group, in New York, has been getting smaller, so that to-day the three-phase reconstruction operation is used on three out of four of the cases which, before the war, we should have fused.

DR. EDWARD W. BOLAND (*Los Angeles, Calif.*): We have all profited greatly in hearing *how* reconstructive operations for the knees in rheumatoid arthritis may best be performed. There are many of us here, I am sure, who are just as interested in *when* such procedures should be undertaken in relation to disease activity as it affects the disease in general and the involved joints in particular.

DR. PRESTON: I don't think that the sedimentation rate or other evidences of systemic activity need to be considered too seriously. What is important is the severity of the rheumatoid activity in the joint which is to be treated, which isn't necessarily the same as the level of the systemic rheumatoid activity.

Of course, it is undesirable to do an extensive surgical correction on a joint that is the seat of acute rheumatoid inflammation, but with this exception, I feel that these joints should be operated promptly. I see no reason for waiting for years for the disease to "burn out". The end-results of cases which operated while the disease was active do not indicate that this delay is necessary. By rehabilitating the patient promptly, years of invalidism is avoided.

MODERATOR KEY: I would go further than that, and say, do it as soon as you can get the patient's consent. The earlier you do it, the less surgery you have to do, and the better your result is going to be, provided you can continue after-treatment and prevent a recurrence.

Frank Dixon used to feel (and I imagine he still does, and I think he has good grounds for it) that operating on these acutely affected joints sometimes arrests the progress of the disease, just as they used to take tonsils out and cure rheumatoid arthritis—or at least get a remission, probably through a change in the physiology of the individual resulting from the anaesthetic and the surgery.

I do not feel that you should wait until the arthritis is cured, because by that time the patient may be amenable to help but not to correction.

Reconstructive Surgery of the Hip in Arthritis. By CARL E. BADGLEY, *Ann Arbor, Mich.* (By invitation.)

Reconstructive surgery of the hip in arthritis produces at its best a poor substitute for a normal functional hip, but many procedures have been helpful in alleviating pain and diminishing disability.

Extra-Articular Procedures have been many and varied. Correction of flexion and adduction contractures by soft tissue release and by osteotomies have temporarily benefited for short or occasionally long periods. Forage of the neck and head of the femur has improved some cases sufficiently to encourage some clinicians. Others have tried to de-nervate the hip joint.

Intra-Articular Procedures. Acetabuloplasty and cheilectomy have not been successful with sufficient frequency to warrant their use. Pseudarthroses of the hip relieve pain, but with considerable loss of function. Arthroplasties of the hip or the substitution for the head and neck of the femur of a mechanical prosthesis have been successful in some. Arthrodesis of the hip with fusion is most successful for standing and walking, but difficult for sitting.

Discussion.—MODERATOR KEY: The single most useful therapeutic measure in osteo-arthritis of the hip is to persuade the patient to use a walking stick and rest the hip, and the older I get and the more I see of the hips I have operated on to restore movement, the fewer operations I recommend. Dr. Badgley has shown a good one, and I have a few good ones too, but I have a lot more poor ones. We don't show those, but they show themselves to us, and we cannot always be sure that the patient is going to be better when you have finished than before you started.

Weight reduction and exercise are also important.

Hydrocortisone Injected into Degenerated Intervertebral Disks. By HENRY L. FEFFER, *Washington, D.C.* (introduced by J. J. Bunim).

Although degeneration of the intervertebral disk is an insidious process beginning in the second decade of life, acute clinical episodes are probably associated with sudden increases in intranuclear pressure. Protrusion of the disk thus is governed by the fluid balance within the nucleus pulposus, and symptoms are produced by tension on the posterior longitudinal ligament and adjacent spinal nerve roots.

In view of the universally accepted value of intra-articular hydrocortisone therapy in degenerative joint disease, it was felt that the drug should have a similar anti-inflammatory action on the intervertebral disks. Sixty patients with suspected disk disease as well as controls were treated by combining a nucleogram with the injection so that all results could be interpreted in the light of the pathology illustrated.

Of the sixty patients, 55 had pathological disks and in 37 (67 per cent.) rapid remission was achieved. The response has been permanent in all but four for a maximum follow-up period of 8 months. Sixteen of the eighteen patients who were not relieved were surgically explored, and all demonstrated gross ruptures through the annulus fibrosus.

Discussion.—DR. THOMAS MCP. BROWN (*Washington, D.C.*): I think we are all interested from several points of view. Sometimes conservative measures may be worth while, and at other times we should advise early operation to avoid permanent difficulties.

Finally, we recognize those cases in whom the disease is apparently present, at least in whom the herniation is obviously present in the myelogram, who at operation reveal very little; some of these individuals later experience great back pain, possibly to some degree furthered by the operative procedure.

The most important thing presented by Dr. Feffer is a diagnostic tool to separate these two groups.

From the therapeutic point of view we have the interesting fact that a single injection will do so much good; this separates this group from those with peripheral articular involvement requiring repeated injections.

Has Dr. Feffer any plans to study the pathophysiology of the alteration induced by this single-injection method?

DR. FEFFER: Dr. Brown, physiologically, the intervertebral disk encloses a gel confined within the annulus fibrosus. It swells as the gel swells by inhibition in response to stresses and strains, and shrinks when those strains are relieved.

The swelling of an intervertebral disk in the pathological state is evidently different and is related to the drawing in of surrounding fluid through the cartilaginous end-plates because of an increased osmotic pressure within the disk. This is probably a depolymerization effect and since the chondroitin sulphate, which is the predominant polysaccharide in the nucleus, is extremely sensitive to the slight changes in *p*H, I am trying to figure out, at this time, an electrode which would make *in vivo* studies feasible. This might give us more insight into the actual nature of the pathological physiology than any other form of investigation.

DR. WILLIAM H. GOODSON (*Kansas City, Mo.*): Were myelograms made before the injection?

DR. FEFFER: The severe ones had only nucleograms or discograms, and most of us feel these are routinely more accurate than the myelogram, which produces about 20 per cent. false negatives. There were some with negative myelograms who continued to have a typical clinical disk picture. When these were subjected to that procedure a good percentage showed a degenerated or herniated disk.

DR. J. ALBERT KEY (*St. Louis, Mo.*): If this work can be substantiated, Dr. Feffer has certainly made a very important contribution to the low-back problem. We do not cure all those we operate on by any means, and he achieves nearly as many cures as we do. I do not know how many patients are benefited to a point where life is more tolerable. Such patients are extremely important because those that we fail to help are usually the ones that this procedure does help. Apparently, by this method, we may be able not only to diagnose them beforehand, but also to cure a high percentage of those which we have not been able to cure by surgery.

We tried the discogram about 2 years ago. We used a 26-gauge needle, which is the one recommended, and we had such a hard time doing it that we gave it up. Dr. Feffer is bolder and uses a bigger needle, and I think maybe I can go home and try again.

DR. FEFFER: Dr. Key's comments brought to mind the subject of recurrences. I have recently heard of a patient who was operated upon by a neurosurgeon without his knowing that I had been in the picture before. I had injected only the fifth lumbar disk which was degenerated, and the patient had recovered, but 3 months later he had a recurrence, and on exploration the recurrence was found to be at the level of the fourth lumbar disk. The fifth was normal. This proves that the vagaries of the whole disk picture with its multiplicity of involvement can confuse diagnosis and ruin the surgical result.

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Rehabilitation of the Arthritic Hand. By RALPH A. JESSAR and ERNEST M. BROWN, JR., *Philadelphia, Pa.*

Since disabilities of the hands of the rheumatoid arthritic patient are the results of inflammatory involvement of the small joints and soft tissues and tendons of the hands, an attempt was made to develop a technique whereby the disability and deformity might be reversed or arrested. The following sequence of events represents the pathogenesis of the hand deformities:

(1) Inflammation of the small joints of the fingers with the resultant joint effusion and distension.
(2) Prolonged joint effusion and concurrent distension allows stretching of the ligamentous fibrous tissues of the joint with subsequent subluxation.
(3) Subluxation is maintained by the muscles of the flexor groups.
(4) Flexion contractures occur and are maintained by a secondary stenosing tenosynovitis affecting the flexor muscle tendons.
(5) Concurrent inflammatory involvement of the hand muscles leads to atrophy and disuse promoting further hand deformities.

Since these hypothetical changes might be susceptible to modification or reversal, an attempt was made, using intrasynovial hydrocortisone, infusion and distension of

the flexor tendon sheaths of the hands, and intensive physiotherapy, to rehabilitate the involved hands of a limited number of rheumatoid arthritics. In a small number of patients it has so far been possible to correct, at least partially, acute ulnar deviation, early spindle-shaped deformity of the proximal interphalangeal joint, "grasshopper deformity" of the fingers, and stenosing tenosynovitis of the flexor tendons. As a result of these studies, it is believed that if sufficient attention is paid to the reversibility of early inflammatory lesions of the joints, tendons, and soft tissues of the hands in rheumatoid arthritis, late deformities and disabilities may be for the most part prevented or corrected.

Osteo-Arthritis of the Cervical Spine. Stages and Treatment. By JOHN G. KUHNS, *Boston, Mass.*

Symptomatic osteo-arthritis of the cervical spine is found in about 10 per cent. of the patients seen in an arthritic clinic. Usually the disease shows gradual progression both in pathological changes and in symptoms. Three stages can be recognized: early, moderately advanced, and late. In the early stage the symptoms are usually those of muscular sprain, and treatment chiefly consists in support and physiotherapy. In the moderately advanced stage the symptoms are usually neurological in character, and symptoms are relieved by traction on the cervical spine, firm support to the neck, and relief of pressure upon the nerve roots by surgery. Displacement of degenerated intervertebral disks is rarely demonstrated, although gradual disappearance of the disks is common. In the late stage, irreversible changes are frequently found in the cervical spine, and symptoms are usually both mechanical and neurological. Three types of end-stage are observed: bony bridging with extreme limitation of motion, forward subluxation of a cervical vertebra with disappearance of the cervical intervertebral disk, and osteoporosis with vertebral collapse. Treatment is symptomatic, usually consisting in rigid support of the cervical spine.

Discussion.—DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): Has Dr. Kuhns any observations on the occupation of patients with severe symptoms from degenerative arthritis of the spine. A recent resident in our clinic from Calcutta, India, became quite interested in the high increase of back symptoms in our rather "lightly laden" clientèle. He, therefore, studied a group of Hindu porters in Calcutta by careful history and *x*-ray studies of the spine. He found that none of these porters had ever had pain referable to the spine—not even a "pain in the neck"!

In a similar study of our cases, for every common labourer who has come to the Arthritis Section with pain in the back, there has been at least one physician.

DR. KUHNS: There is no direct correlation with occupation. People who sit and bend over are affected much more frequently than those who live their lives in a more erect position. This we have thought was the result of posture or static stresses and less good muscular development in the antigravity muscles of the neck.

DR. STEPHEN J. WALKER (*Whitesboro, N.Y.*): During the past 15 years I have seen a great number of cases of osteo-arthritis of the cervical and lumbar spine, and have treated them on the same principles as Dr. Kuhns.

I should like to bring to your attention a product, which has not yet found its proper place in our armamentarium, called Endogen A*. I started using it in the 1920s and it has done wonders for the majority of these patients ever since.

Nobody seems to know exactly the rationale of the effect of Endogen A, although the role of casein and peptone as well as colloidal sulphur is obvious. I have always used it in conjunction with salicylates, and, more recently, with Butazolidin in the therapy of most forms of osteo-arthritis. In the early stages of the disease I give one ampoule twice a week and reduce the dosage gradually to one ampoule weekly until the patient's condition is definitely improved. All other supportive measures, such as diet, rest, and an optimistic outlook for the future are equally important in treatment.

DR. KUHNS: I have observed temporary improvement after injections of a number of substances. A number of my medical colleagues will give oestrogens, or testosterone, and in most instances the patients become temporarily better. There are many physiological and metabolic factors in this disease which we do not understand.

DR. PHILIP R. TROMMER (*Philadelphia, Pa.*): Why does cervical traction sometimes aggravate the condition?

DR. KUHNS: I have observed this phenomenon, but I do not know that I can give you any definite answer.

There are many ways of giving traction. I have been surprised that nobody has brought me to task for not giving heavy intermittent traction in the upright position. There are many other ways; some of my colleagues give it at 45°. When our type of traction does not work, we usually change the direction of the pull, feeling that we are not relieving the pressure by the supine position.

DR. PHILIP R. TROMMER (*Philadelphia, Pa.*): I am reminded of an answer that was given at the last Congress of Physical Medicine in Washington. They pointed out that the spurs came from the neuro-canal pointing downwards, and that when you put traction up it made the angle much larger.

They pointed out that the nerve canal is like a sleeve. You have a spur here and if you pull on the nerve and put traction up here, you are aggravating the situation.

I have tried it on some by stretching the neck by hand; if that makes them worse, we do not use traction.

Controlled Therapy of Degenerative Arthritis. By EUGENE F. TRAUT and EDWIN W. PASSARELLI, *Chicago, Ill.*

The various forms of chronic arthritis have a fluctuating natural history characterized by remissions, relapses, and progression. The importance of the psyche in the pathogenesis and course of arthritis is increasingly apparent. On these accounts and to satisfy the natural desire of the patient to initiate treatment at his first visit, we decided to fashion a base line by placebo therapy. Besides serving as a control on effects of other measures, placebos would not interfere with such laboratory procedures as measurement of the uric acid level in the serum, the sedimentation rate of erythrocytes, or the various serological tests. The placebo procedures instituted were lactose tablets and subcutaneous injections

* Manufactured by Endo Products, Inc., Richmond Hill, N.Y. It is available in 2-ml. ampoules containing a solution of 50 mg. casein, 60 mg. peptone, and 5 mg. colloidal sulphur.

of saline. The tablets were exhibited first. If the patient failed to be improved by tablet placebo or was benefited initially only to fail to improve later, the injection placebo was instituted. The patients were interviewed and examined as to their progress by six rheumatologists, each being careful to maintain a casual, non-suggestible attitude. The results were described by the patients and also obtained by inquiry and by physical and laboratory examination. Data were broken down according to race and sex.

Over 182 patients with degenerative arthritis were studied in this manner for one and a half years. More than half of those receiving lactose tablets experienced relief, justifying continued visits to the clinic and the abandoning of previously used salicylates and proprietary preparations. Those initially unresponsive to tablets and those eventually ceasing to improve on tablets were treated by subcutaneous injections of normal saline solution. Approximately the same percentage of the patients not helped by tablet medication responded favourably to the salt-water injections. There was a sex and race difference in placebo response, and the difference in severity of joint involvement also affected the response. The combined tablet and injection procedures satisfactorily helped significantly 75 per cent.

The conclusion is drawn that such a controlled placebo study is necessary in determining the fitness of newly-proposed treatments to enter our already too large pharmacopoeias and textbooks.

Discussion.—DR. OTTO STEINBROCKER (*New York City*): Any effort to control therapy is a very commendable procedure. I was not able to tell from this interesting discussion whether any attempt was made to correlate the patient's symptoms and the objective findings. I would state from our own experience with so-called osteo-arthritis that it is important to establish the diagnosis on the basis of clinical signs as well as on *x*-ray appearances and the patient's complaints.

It is pretty widely accepted now that there are placebo reactors, and I think the information presented can be valuable if it is correlated with the clinical evaluation of the disease itself as well as with the symptoms.

DR. TRAUT: The correlations mentioned were made, and due observations and findings were recorded. The subjective complaints were relieved in a larger measure than the objective findings. It is quite remarkable that an individual would come in who could not raise his shoulder, and that after a placebo he might move his arm freely. This motion was helpful as spasm was lessened.

Resorptive Osteopathy in Inflammatory Arthritis. By MURRAY SILVER and OTTO STEINBROCKER, *New York, N.Y.*

Atypical clinical pictures of arthropathy in different forms, based on extensive destruction or mutilation of bone, have been described in sporadic reports for many years under a variety of confusing names, such as "arthritis mutilans", "absorptive arthritis", and "opera-glass hand". Five cases with inflammatory arthritides associated with great resorption of bone, two with biopsies of articular structures, provide the material for this report. They suggest the need for a better understanding of this unusual manifestation of the arthropathies.

That such lesions do occur in different forms and in almost any site is another reflection of the diverse nature of the arthritides. These bone lesions may simulate other pathological processes, particularly cysts and neoplasms. They may baffle the radiologist and clinician if it is not recognized that single or multiple bones may be extensively resorbed in a variety of ways and degrees in the inflammatory rheumatic disorders. Similar changes, which have received little attention, may be encountered in degenerative lesions of joints and bones.

Our series includes three types of radiological alteration. In the first there may be seen resorption of as much as one half to a whole phalanx, or multiple phalanges. One or more of the carpal bones may be affected alone, or in addition to the phalangeal changes. The classic example of such marked bone resorption involves the fingers to produce the "opera-glass hand", or the telescoping of the phalanges of one or more digits. In the second type, the long bones are involved with small and large osteolytic lesions, cyst-like in some instances, at times extending into the marrow. In the third form, there may be tapering and disappearance of large portions of the long bones, a diffuse resorption, retaining a striking and nearly uniform architecture of the residual bone, with a peg-like appearance at the affected portions. These alterations may occur in multiple forms in some cases.

The non-specific nature of the pathological process is described. Of our five cases, one suffered from psoriasis with arthropathy, one from ankylosing spondylitis with root joint involvement, and the others from rheumatoid arthritis.

Discussion.—DR. SWIFT (*Chicago, Ill.*): I am very much interested in the first case that was presented and I wonder if this patient had psoriasis. We have a case in the ward of an elderly woman who has had psoriasis of the elbows for years, with a telescopic thumb.

Another observation of interest is that a case has recently come into our out-patient clinic which looks like advanced osteomyelitis. On *x* ray, the similarity was striking, and this paper warns us to be on the lookout for other diseases.

DR. SILVER: The patient described did not have psoriasis, but there are other cases in the literature in which psoriasis was associated with "opera-glass hand".

DR. CUMMINGS (*Rochester, N.Y.*): Was parathyroid disease ruled out?

DR. SILVER: The calcium, phosphorus, and alkaline phosphatase determinations were normal in these patients. Hyperparathyroidism can thus be ruled out because one would expect biochemical alterations in the presence of bone disease due to this cause.

Dynamics of Normal and Arthritic Joints (cinematic demonstration). By R. H. FREYBERG, E. RUDD, ARTHUR POST, with the technical assistance of W. CARLIN and G. KLOOS.

A recently-developed means of electronic intensification of fluoroscopic images, has made possible a moving-picture demonstration of joints in normal persons and in patients with arthritis as seen with the fluoroscope. The candle power is intensified by 1,000, so that these

films can be made in the same way as *x* rays of the chest and the patient does not receive excessive radiation.

One difficulty involved in making these films is that the size of the field is limited to a diameter of about 5 inches. A knee joint thus just about covers the field and if the movement takes it off the central beam, the fluoroscopic image is lost. One can expose the film at 64 frames a second and show it in slow motion, so that all subtleties show up very exactly.

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The following papers were also presented but not read:

Long-Term Course of Patients with Rheumatoid Spondylitis treated with Roentgen Therapy. By KEITH H. AVERILL, IVAN F. DUFF, HENRY ZEVELY, W. D. ROBINSON, and ISADORE LAMPE, *Ann Arbor, Mich.*

Effect of Butazolidin (Phenylbutazone) Levels in the Plasma on the Response to Mercurial Diuretics. By HAROLD BROWN and ROBERT S. WARNER, *Salt Lake City, Utah.* (Introduced by John C. Nunemaker.)

Gout in 190 Patients with Emphasis upon Race, Heredity, and Socio-Economic Factors. By HENRICH G. BRUGSCH, MICHAEL G. PIERIK, and JACOB H. YULES, *Boston, Mass.*

Distribution Patterns for Rheumatic Symptoms and Signs. By S. COBB, J. R. ROSENBAUM, J. E. WARREN, and W. R. MERCHANT, *Pittsburgh, Pa.*

Clinical Application of Ivalon Knee Arthroplasty. By MILTON C. COBEY and ANTOINETTE POPOVICI, *Washington, D.C.*

Juvenile Mono-Articular Arthritis; Divergent Form of Rheumatoid Disease. By PAUL H. CURTISS, JR., and RALPH I. WEDGEWOOD, *Cleveland, Ohio.*

Preliminary Clinical Trials with Metacortandracin; Comparative Antirheumatic Potency, Metabolic Activity, and Hormonal Effects. By J. R. DORDNICK and E. J. GLUCK, *New York, N.Y.* (see p. 445).

Spectrophotometric Determination of Antistreptolysin-O. By HARRY A. FELDMAN and ANNE L. GILLEN, *Syracuse, N.Y.*

Treatment of Acute Rheumatic Fever with Metacortandracin. By HARRY A. FELDMAN and LEO JIVOFF, *Syracuse, N.Y.*

Penicillin Prophylaxis in Rheumatoid Arthritis. By PAUL O. HAGEMANN, *St. Louis, Mo.*

Niacin Furfuryl Test and Pathogenesis of Rheumatoid Arthritis. By GEORGE G. HAYDU, *New York, N.Y.*

Correlation of Pain and Radiological Findings of Degenerative Joint Disease of the Cervical and Lumbar Spine. By ALLEN E. HUSSAR and EMANUEL J. GULLER, *Montrose, N.Y.* (Introduced by Howard F. Polley.)

Technique and Rationale for a Routine Comprehensive Physical Examination in Cases of Chronic Musculoskeletal Pain. By J. H. IRVINE, *New York, N.Y.*

Incidence of Positive L.E. Preparations in Patients with Rheumatoid Arthritis. By W. K. ISHMAEL, J. N. OWENS, JR., and R. W. PAYNE, *Oklahoma City, Okla.*

Treatment of Various Rheumatic Conditions with Metacortandracin. By WILLIAM H. KAMMERER and RUSSELL L. CECIL, *New York, N.Y.* (see p. 445).

Treatment of Scleroderma, Sclerodactylia, and Calcinosis by Chelation. By RUBIN KLEIN, *Brooklyn, N.Y.* (see p. 445).

Morphological and Physiological Study of Tissue Cultures of Human and Mammalian Synovial Membranes. By DAVID H. KLING, GLADYS CAMERON, and MILTON G. LEVINE, *Los Angeles, Calif.*

New Methods for the Study of Synovial Fluid in the Diagnosis and Treatment of Arthritis. By DAVID H. KLING and MILTON G. LEVINE, *Los Angeles, Calif.*

Pathology of Experimental Frostbite with particular reference to Cold-Induced Arteritis, Periostitis, and Arthropathy. By J. P. KULKA, J. R. BLAIR, and R. SCHATZKI, *Boston, Mass.*, and *New York, N.Y.*

Effect of Intravenous Colcemide on Acute Gout. By WILLIAM C. KUZELL, RALPH W. SCHAFFARZICK, and W. EDWARD NAUGLER, *San Francisco, Calif.*

Local Cutaneous Response to Nicotinic Acid and Esters as a Diagnostic Aid for Rheumatoid Arthritis. By PAUL LEIFER and ROBERT C. BATTERMAN, *New York, N.Y.*

Studies in Osteo-Arthritis, using Intra-Articular Temperature Response to Injection of Hydrocortisone Acetate. By ROBERT MOORE and JOSEPH L. HOLLANDER, *Philadelphia, Pa.*

Simulated Acute Surgical Abdominal Catastrophe in Systemic Lupus Erythematosus. By VICTOR E. POLLAK, ROBERT C. MUEHRCKE, ROBERT M. KARK, and IRVING E. STECK, *Chicago, Ill.*

Butazolidin. WILLIAM B. RAWLS, *New York, N.Y.* (see p. 444).

Metacortandracin in Diffuse Scleroderma (Systemic Sclerosis). By GERALD P. RODNAN, ROGER BLACK, ALFRED J. BOLLET, and JOSEPH J. BUNIM, *Bethesda, Md.*

Ascorbic Acid and Dehydroascorbic Acid Levels in Plasma in Rheumatoid Arthritis. By MARIAN W. ROPES and MALCOLM THOMPSON, *Boston, Mass.*

Management of Toxic Side-Effects of Phenylbutazone and Cortisone with Emphasis on Ulcer Formation and Water Retention. By DAVID RUML, CHARLES W. DENKO, and DELBERT M. BERGENSTAL, *Chicago, Ill.*

L.E. Phenomenon in Rheumatoid Arthritis. By CHARLES H. SLOCUMB, CLETUS T. FRERICKS, GERTRUDE L. PEASE, HOWARD F. POLLEY, and L. EMMERSON WARD, *Rochester, Minn.*

Joint Changes in Paget's Disease. By IRVIN STEIN and MARTIN L. BELLER, *Philadelphia, Pa.*

Comparison of Rheumatoid Spondylitis and Crippling Fluorosis. By CHARLES LEROY STEINBERG, DWIGHT E. GARDNER, FRANK A. SMITH, and HAROLD C. HODGE, *Rochester, N.Y.* (see p. 378).

Experiences in the Use of Metacortandracin in Disseminated Lupus Erythematosus and Periarteritis Nodosa. By CHARLES LEROY STEINBERG, ANDRIES I. ROODENBURG, and MILTON G. BOHROD, *Rochester, N.Y.*

"Diabetogenic" Properties of Metacortandracin, Hydrocortisone, and Cortisone Acetate—A Comparative Study. By CARL STEVENSON, F. W. MCCOY, and R. H. FREYBERG, *New York, N.Y.*

Rheumatoid Spondylitis: Course and Socio-Economic Significance. By ROBERT L. SWEZEY, JAMES L. PATTERSON, JR., STANLEY MARCUS, JOHN E. MEIHAUS, DAVID A. STRANGE, and MELVIN H. LEVIN, *Los Angeles, Calif.*

Relationship of Sydenham's Chorea to Infection with Group A Streptococci. By ANGELO TARANTA and GENE H. STOLLERMAN, *New York, N.Y.*

Another Concept and Syndrome in Rheumatic Disease. By G. DOUGLAS TAYLOR, *Toronto, Ont.*

Osteogenesis Imperfecta Tarda. By STANLEY L. WALLACE, PHILIP VIGODA, and HOWARD EASLING, *Selfridge Air Force Base, Mt. Clemens, Mich.*

Punch Biopsy of Synovial Membrane of the Knee in Diagnosis of Joint Disease. By HENRY A. ZEVELY, *Ann Arbor, Mich.* (Introduced by Ivan F. Duff.)

BOOK REVIEW

La spondilite anchilosante. By Tommaso Lucherini and Claudio Cervini. 1955. Pp. 469. Edizioni Mediche e Scientifiche, Rome. (L. 4,500; 50*s*.)

This volume of over 400 pages (15 chapters), which is claimed to be the first comprehensive work on ankylosing spondylitis in Italian, has been compiled by the director of the Rheumatological Institute of Rome University and his assistant. Excellent colour-plates, photographs, glossy paper, and an imposing array of indices, all combine to ease the task of the reader. The authors' own experience is based on a study of 215 cases (202 men, 13 women) and results are carefully tabulated. Much industry, too, has gone into the presentation of material known to the authors to be controversial. A map of Italy, for example, illustrates the incidence of the disease in various provinces, and one is struck by the figure of "46" for the Rome area and a "nil return" for, say, southern Sardinia. But the authors are the first to admit that the chronicity of the disease and the presence of a well-equipped Institute in the capital may have an important bearing on the results.

It is pleasant to read of the prominent role played by British rheumatologists, and on turning the pages one occasionally gets the impression that one is going through a list of the senior members of the Heberden Society. A fitting tribute is paid to the pioneer work of the late Gilbert Scott, it appears that out of some forty names suggested for the disease in the past 100 years, that of Buckley (1935)—"ankylosing spondylitis"—is the one favoured by the authors. Therapy, in general, follows British lines but, as is inevitable in a work of this kind, reference is made to methods untried by the authors, some of which (*e.g.* the injection of Thorium-X and its probable deposition in organs such as the liver) would be rejected by an intelligent patient. One is somehow reminded of the old story about George Bernard Shaw and the lady who consulted him because her dog was misbehaving in the house. G.B.S. advised the lethal chamber. "But are you sure he would use it?" asked the lady.

It has now become customary to append summaries in at least two foreign languages and the authors have supplied them in Italian, French, English, German, and Spanish. Foreign papers have been developing a curious tradition in these summaries. They use impeccable French and German but insist on what may be called dutch-bulb-catalogue English. Thus, "tombant d'accord avec les auteurs suédois . . . qui ont apporté des contributions au sujet . . .", and "darin auch mit den schwedischen Forschern . . . übereinstimmend . . .", becomes in English (quoting the whole sentence)—"The authors, agreeing in this even with the Swedish research workers (Engfeldt *et al.*), who have added recently to the argumentative material, think that at the bottom of the apparent, harsh contrast between the findings of a phlogistic imprint, and respectively, degenerative, by the different workers mentioned above, and hence, the different evolutive phases in or during which the various observations befell." Fortunately, the English summary is no guide to the quality of the contents, and a perusal of the bibliography alone (given at the end of each chapter), suggests that it covers all major contributions to the subject.

DAVID PREISKEL.