AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1956

The Annual Meeting of the American Rheumatism Association was held at Chicago, Illinois, on June 8 and 9, 1956, under the presidency of Dr. Charles L. Short of Boston. Abstracts of 30 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. Panel Discussions were held on “Gout” (Moderator: Dr. A. Gutman) and on “A Teaching Collection of Lantern Slides illustrating the Pathology of Arthritis and Rheumatism”, the work of a Sub-committee of the Arthritis and Rheumatism Foundation (Moderator: Dr. Currier McEwen). A report on “Proposed Diagnostic Criteria for Rheumatoid Arthritis” was presented by the Committee on Diagnostic Criteria (Chairman: Dr. Marian W. Ropes).

PRESIDENTIAL ADDRESS

BY

CHARLES L. SHORT

President of the American Rheumatism Association, 1955-56

The presidential addresses delivered before this association have usually dealt with a clinical or scientific subject of special interest to the speaker at the time or with broad and general aspects of teaching and research in the rheumatic diseases. Only a few have considered in some detail the activities and aims of your association—subjects with which I have been intimately concerned during the past year, and which I wish to discuss this afternoon in a brief and necessarily incomplete form.

Just 10 years ago, in May, 1946, the American Rheumatism Association assembled in New York for what was aptly termed a Reunion Meeting. During the war years, no meetings had been held and no new members added. The affairs of the society had been in the custodial care of the Officers and Executive Committee while the greater part of the membership was scattered far and wide in the armed forces. In his presidential address at this meeting, Dr. W. Paul Holbrook, took the opportunity to present what he called major goals or challenging opportunities for accomplishment by the association and its membership. These goals were four in number. While successfully achieved in part, they bear repetition and re-emphasis a decade later, along with additional comments provoked by the changing outlook in which we have all shared on the still elusive search for the cause and cure of the rheumatic diseases.

I should like to mention one goal first, perhaps because it has been achieved so magnificently and I am sure beyond the expectation of the membership 10 years ago. This is what Dr. Holbrook modestly called a strengthening of the work in public relations, with the eventual development of a fund-raising organization. Within 2 years the Arthritis and Rheumatism Foundation was established. In another 2 years, by the combined efforts of the Foundation and our own Association, the National Institute working in the field of metabolic diseases was expanded to include the field of rheumatism and funds were appropriated by Congress to carry on this augmented work. We are now blessed with the happy co-operation of professional, voluntary, and governmental groups, all concerned with a common objective, the alleviation and eventual prevention of a group of chronic disabling diseases.

It is unnecessary to list in detail to this audience the contributions made by the Arthritis and Rheumatism Foundation, both nationally and locally, to an improved outlook for the rheumatic patient, not only at this time, by the education of those concerned with his care, but also in the future, by the financing of clinical and basic research. To quote just two figures, the amount expended for such investigations in the United States has increased from $300,000 yearly in 1948 to $3,000,000 in 1955. No statistical tests of significance are necessary to assume an association between this increase and the operations of the Arthritis and Rheumatism Foundation and the National Institute for Arthritis and Metabolic Diseases.

A second major goal set 10 years ago was the education of physicians in the basic treatment of arthritis. The last 6 years’ experience with suppressive agents, valuable as they are in selected cases and as research tools, has failed to diminish the importance of measures generally believed to be helpful in the management of a disease like rheumatoid arthritis. I say “generally believed to be helpful”, because the value of rest, salicylates, simple forms of physical therapy, non-operative orthopaedic measures, and above all the study and treatment of the patient as a human being, has yet to be established by...
controlled therapeutic studies. Nevertheless, few of us would wish to discard such measures, whether or not suppressive agents are also used. To supply the practitioner with the knowledge and will to prescribe these methods in a specific and detailed fashion is no easier task to-day than it was 10 years ago. In addition, we have the obligation of pointing out the proper indications for suppressive treatment, along with warnings against its injudicious or unwarranted use. Certainly these objects have begun to appear within closer reach through the educational programme of the Arthritis and Rheumatism Foundation as related to the practitioner. The Bulletin on Rheumatic Disease, the Primer, and the Rheumatism Review, while created by our member, could never have received their present wide distribution to the medical profession, nor could our exhibits have been financed without assistance from the Arthritis and Rheumatism Foundation. Valuable as these methods are, our personal contact with the practitioner should provide opportunity for more vivid and effective forms of instruction. These include not only talks at society and staff meetings and the careful teaching of trainees and of physicians assisting in arthritis clinics, but especially our teaching in regard to diagnosis and patient management as consultants. If the referring physician is given a detailed, conscientiously prepared outline of the problems presented by an individual patient and their best solution, he should gradually but surely be able to apply what he learns to other cases of rheumatic disease encountered in his practice.

In 1946, only one local rheumatism society was affiliated with the American Rheumatism Association. This was the New York Rheumatism Association, which was host to the parent society at the Reunion Meeting. The third major goal was the organization of affiliated societies “in every community that can support one”. A substantial growth in their number has taken place since then, the present total being 25. Six have been added in the last year, largely through the effective efforts of the Committee on Affiliation with Local Societies. But since there are still 25 states without such a society, the challenge still lies before us.

The fourth major goal was “a wise and progressive enlargement of membership”. As shown in Fig. 1, the membership has steadily increased, with a recent spurt due to the personal efforts of our last year’s president. We still need more new members representing the widely varying interests of those now concerned with the study and treatment of rheumatic disease. The Table brings out the latter point; the first column lists those whose purpose is to help the rheumatic patient more effectively and the second those primarily concerned with the advancement of knowledge in this field.

Most rheumatologists, or rather most internists with a major or substantial interest in musculoskeletal disease, are already among our members. We must be on the look-out, however, for additional members from this group, whether younger or older, once it is clear that their interests lie in this direction.

Since rheumatic disease frequently contributes to disability in our aging population and may be incapacitating or even fatal in childhood, geriatrists and pediatricians, who are fundamentally internists, should be brought into our membership.

The question may be raised whether the general practitioner or generalist belongs in the society. I feel that a certain number do, along with internists for whom rheumatism represents only one facet of their practice. Such individuals can learn and be stimulated by attendance at our meetings, and can also contribute to them by their clinical observations of early and atypical disease and their unique privilege of following certain patients through a lifetime of practice.

I include the radiologist because the clinical members of our society rely on his skill so often in their diagnoses, but, as far as I can recall, it is some time since a distinctly radiological communication has been read at one of our meetings.

Orthopaedists are among the founding fathers of the Society and, in addition to their contributions to recon-

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normal is defined, we can better interpret the
alterations produced by disease. This approach requires
the use of modern analytical methods, including those
developed by physicists and applied by biologists.
I have used the term biologist in the list to denote that
the investigator in this field need not be restricted to a
single discipline. It has been suggested, for example, that
the embryological approach deserves more attention and
that information about the development of the connective
tissues in an embryonic stage may be important in the
study of both normal and abnormal healing, regeneration
and growth. It may be hoped that this society will
continue to attract to its membership the connective tissue
biologist, who surely looks for clinical corroboration in
many of his problems and desires to see his work eventually
reach useful application.
Most of the papers on our early programme of
fundamental nature were concerned with bacteriology
and immunology, and to-day workers in these fields
continue to contribute an important part of the basic
exploratory work in rheumatic disease.
The pathologist not only remains indispensable as a
partner in clinical and fundamental investigation but can
also furnish important clues to the origins and
mechanisms of disease by the methods of classical
histology.
The pharmacologist is finally listed since his contribu-
tions may become greater as the number of agents
suppressing connective tissue inflammation increases.
To repeat the original premise, a carefully selected
increase in membership is one of our major objectives.
May this incomplete check-list prove useful in the recruit-
ing by each one of you of new members who can con-
tribute by their special talents to the aims of the associa-
tion and in turn receive assistance in the successful
accomplishment of their clinical or scientific endeavours.
I should finally like to discuss briefly the nature and
content of our scientific programmes (Fig. 2, opposite).
I have divided the papers given at the annual meetings
(invited speakers being excluded) into three categories:

The topmost division refers to fundamental studies; these
nature of connective tissue and its chemical or physical
alterations in health and disease; fundamental aspects
of infection and immunity in relation to rheumatic disease;
purely laboratory research including experimental
arthritis.
The middle division is made up of clinical investigation;
and embraces epidemiological studies and controlled
therapeutic trials as well as the use of laboratory tech-
niques.
The lowest division, not necessarily the least important,
includes purely clinical aspects of connective tissue
disease.
Each whole block represents an era in the life of the
Association, the first encompassing the pre-war years and
the next two sharing the 11 years since meetings were
resumed after the war. For comparison, an analysis of
the papers presented at the two Interim Sessions is shown
in this fourth block. In each block, the mean unweighted
percentages are given of papers in the three categories.
No startling conclusions are to be drawn from this figure, which I shall interpret with caution since it was not prepared with the aid of a biostatistician. Papers on clinical investigation have continued to make up about 40 per cent. of those presented, while the proportion of purely clinical papers has slightly decreased and those devoted to fundamental studies have increased. There is an obvious bias in the percentages for the Interim Sessions, in that members and research fellows who are not yet members have thus far been encouraged to present investigations of a basic nature at this meeting. It will be interesting to see whether this division of the Interim Session papers persists in future years. I am willing to predict that the programmes of the Annual Meeting and of the Interim Session will eventually come to resemble each other more closely.

The criticism has been not infrequently heard from some of our clinical members in recent years that our meetings are too scientific, the fundamental investigators, either more tolerant or less articulate, having apparently failed to bring up the converse. A psychiatric interpretation of this situation has been suggested: that clinicians like myself experience a feeling of inferiority as the complexities of modern biophysical and biochemical techniques are revealed. That thus far clinical studies have failed to disclose specific leads as to the aetiology of the connective tissue diseases hardly seems the main reason for the fundamental approach. It is rather that a better understanding of disease mechanisms and treatment can result only from a greatly extended knowledge of the anatomy, physiology, and reactions caused by disease of the tissue chiefly involved. More important, both fundamental and clinical studies have benefited greatly from the exchange of ideas and constantly stimulate each other. It is highly possible that the next great advance in rheumatism may be derived from careful clinical observation.

In conclusion, it is my hope that the membership of the American Rheumatism Association will become even more representative of all those engaged in the study and treatment of the rheumatic diseases, and that the programme will contain substantial but necessarily varying proportions of papers dealing with purely clinical subjects, clinical investigation, and fundamental research. Little would be gained and much lost by any division of the society or of its meetings into clinical and laboratory units. As the concept of the connective tissue diseases has provided a unifying influence on research in rheumatic conditions, so may the American Rheumatism Association continue as the chief integrating force in the United States towards their eventual solution.


Much has been learned concerning the mechanism in vitro fibril formation in solutions of purified collagen. Attempts to relate this knowledge to fibrogenesis in vivo have led towards efforts to identify precursors of collagen, factors regulating fibril formation, and components responsible for some physical chemical properties of connective tissue.

Cold neutral salt extracts of fresh corium from growing guinea-pigs are very viscous. Electrophoretic diagrams of such extracts, in addition to showing patterns qualitatively similar to that of serum, reveal also a high hypersharp slow-moving boundary in the γ-globulin fraction. An analogous additional peak is found in the ultracentrifuge pattern.

This boundary proves to represent a dissolved collagen fraction in concentrations up to 0-3 per cent. which can be precipitated as a gel of striated fibrils by warming to 37°C. The viscosity of extracts was almost completely destroyed by collagenase in 15 min. at room temperature and was essentially unaffected by trypsin or hyaluronidase at the appropriate pH. Restriction of growth rate by diet was paralleled by reduction in viscosity of the extracts, which in turn was a nearly linear function of the hydroxyproline content. Static weight for 10 days resulted in a 5-10-fold drop in relative viscosity paralleled by an equal fall in hydroxyproline. Starvation for 2 days after a period of rapid growth resulted in a 5-fold decrease in viscosity and hydroxyproline content. Much smaller decreases in tyrosine (non-collagenous protein) and bound hexose unrelated to viscosity were noted. No significant changes were noted in content of hexosamine or uronic acid. Ultracentrifuge and electrophoretic patterns reflect these changes mainly in the collagen peak.

Similar studies on scorbutic tissues now in progress are complicated by this superimposed growth effect. It is concluded that the collagen extracted by neutral salt solutions is derived from the extracellular ground substance and may play an important role in the physiochemical properties of the connective tissue.
Discussion.—DR. MORRIS ZIFF (New York, N. Y.): Have you used starved animals to see whether there is any relationship between the percentage of the soluble extract and the concentration of fibroblasts in the tissue?

DR. GROSS: We are waiting for our histological preparations to be completed. The chemical studies have moved faster.

Influence of Beta-Aminopropionitrile on Developing Connective Tissue. By D. MURRAY ANGEVINE, JOHN E. MIELKE, and JOSEPH J. LALIGH, Madison, Wis.

Synthetic beta-aminopropionitrile (BAPN) when fed to rats may modify the developments of bone, cartilage, and connective tissue. To study the influence of this substance on developing connective tissue, croton oil pouches were produced in rats and the walls of such pouches from test and control animals were examined both histologically and chemically.

33 Sprague Dawley rats, weighing 161 to 187 g. were divided into groups of twelve control rats and 21 test rats which received between 0.15 and 0.20 ml. BAPN per 100 ml. drinking water per day. After 6, 12, and 18 days, rats from each group were were killed and sections taken from the pouches for microscopic study. The remaining pouch tissue was used for chemical studies. The net weight of the test pouches was less than the corresponding control pouches, their exterior was irregular and indistinct from the surrounding areolar tissue, and in contrast to the controls fifteen of the test pouches had collapsed by the end of 18 days.

Microscopically the fibroblasts from the test pouches showed retarded maturation. The connective tissue cells were still rounded and vesicular after 18 days and, in addition, the collagen fibres of the test pouches did not show the usual progression in development or organization with respect to time as did the collagen fibres from the control pouches.

The connective tissue was analysed for hexosamine and hydroxyproline. The values for hexosamine from the test pouches were comparable to those observed in the controls. There was a definite decrease in the hydroxyproline in the test rats which agreed with the microscopic observation of delayed collagen synthesis on microscopic examination.

Biosynthesis of Hyaluronic Acid by Group-A Streptococci. By ALBERT DORFMAN and J. ANTHONY CIFONELLI, Chicago, Ill. (By invitation.)

Previous studies from this laboratory have shown that, with appropriate isotopic precursors, the mechanism of biosynthesis of hyaluronic acid can be studied utilizing a strain of Group-A streptococcus. These studies established the precursors of the fourteen different carbon atoms of the disaccharide-repeating unit of hyaluronic acid. The recent discovery of a series of uridine nucleotides which contain the monosaccharide portions of hyaluronic acid and the demonstration that uridine diphosphoglucose is involved in the synthesis of sucrose and trehalose have suggested that uridine nucleotides may be involved in the biosynthesis of mucopolysaccharides. Glaser and Brown (1955) have reported the incorporation of radioactivity in low molecular weight hyaluronic acid as a result of the action of an enzyme preparation derived from Rous sarcoma on labelled uridine diphospho N-acetylgulcosamine. Similar experiments in this laboratory utilizing streptococcal extracts have led to the incorporation of only small amounts of radioactivity.

A study has been undertaken to attempt to identify possible intermediates in the synthesis of hyaluronic acid utilizing extracts of streptococci. Uridine diphospho-N-acetylgulcosamine and uridine diphosphoglucuronic acid have been identified in these extracts. An additional uridine nucleotide containing an unidentified amino sugar has also been demonstrated. This compound appears to be identical with one of the nucleotides previously isolated by Park (1952) from penicillin-treated staphylococci.

Discussion.—DR. R. J. WINZLER (Chicago, Ill.): I should like to inquire whether Dr. Dorfman has any evidence for the appearance of this new amino sugar-uridine complex in mammalian tissue.

DR. DORFMAN: We have no evidence, and it has so far not been found in mammalian tissue, to my knowledge.

REFERENCES


Characterization of the Proteins from Human Synovial Fluid. By KARL SCHMID and MARGARET E. MACNAIR, BOSTON, MASS.

The proteins of synovial fluid have long been suspected of being identical with those of blood plasma. However, except for the identification of a few protein components by enzymatic or immunochemical methods, no systematic study has yet been carried out to establish the validity of this hypothesis.

The proteins of joint fluid, obtained from patients with rheumatoid and traumatic arthritis and neuro-arthritis, and of plasma from the same individuals, were fractionated simultaneously by two methods. On the one hand, the proteins were separated by electrophoresis and identified by immunochemical reactions (Graber, 1955); on the other, they were fractionated according to their solubility (Cohn and others, 1946, 1950) and characterized by the following properties:

Distribution of the proteins among the fractions, Content of protein-bound carbohydrate and cholesterol, Electrophoretic mobilities and distribution. Ultracentrifugal distribution and sedimentation constants. Specific reactions such as cloting, ion-binding capacity (albumin, β1-metal-combining protein), reaction with cyanide ions (caeruloplasmin), titration of the isagglutinin, diphtheria antitoxin and antistreptolysin-O content, electrophoresis at pH 4.5, and immunochemical reactions by the Ouchterlony technique, using horse serum against human serum.
The results indicated that the proteins of pathological joint fluids are, for the most part, identical with those of plasma. In contrast to these similarities, differences were also noted. Besides variations in the total protein concentration (reported by others), a significant difference was observed in the relative amounts and distribution of the lipoproteins.

Discussion.—Dr. Ward Pigman (Birmingham, Ala.): I should like to compliment Dr. Schmid on doing a very necessary piece of work. In the past it has simply been assumed that the synovial fluid components are very similar to those of other tissues. He has now demonstrated that the major components of arthritic fluids resemble those of blood very closely, as was earlier suspected. However, a considerable body of evidence indicates that, in the arthritic state, blood proteins are able to pass the synovial membrane and mix with the fluid more readily than usual. The real problem is the composition of the normal fluid. I know Dr. Schmid does not have the answer to this, but I think it is worth remembering that this work applies to arthritic fluids, where there is altered permeability and one would expect many blood components to enter the synovial space. What we do not know is what materials are present in normal synovial fluid. I hope that Dr. Schmid is able to continue this fine and tedious work until the full picture is completed.

Dr. Schmid: We are now in the process of studying post-mortem as well as normal synovial fluids. As far as we could determine by electrophoresis at pH 8.6 and 4.5, using hyaluronidase-treated fluid, we got the idea that their proteins do not differ significantly from those of pathological fluids except for the concentration.

In addition, I should like to mention that protein components which exist solely in synovial fluid are not excluded by the investigations I have just reported. For instance, one could imagine that the white cells could possibly release certain forms of nucleic acid. Perhaps one should also consider precursors of hyaluronic acid and collagen. Furthermore, we have noticed a component in Fraction V derived from pathological synovial fluids which is characterized by its yellow colour.

REFERENCES

Experimental Production of Arthritis in Rats. By Carl M. Pearson, Los Angeles, Calif. (Introduced by Dr. Howard J. Weinberger.)
Freund-type water-in-oil adjuvant preparations containing heat-killed mycobacteria were combined with skeletal muscle from rats of the same strain used in the subsequent experiment, and these emulsions were given intracutaneously in the posterior cervical region to rats of the Wistar and Long-Evans strains. After a latent period of 2 to 6 weeks, varying degrees of acute inflammatory swelling developed in the ankles, the small joints of one or several paws, and the joints of the tail. After several weeks, periosteal reactions and exostoses were noted by x-ray in these regions. Histologically the reaction was one of intense granulation tissue proliferation with invasion of bone marrow spaces and the subchondral regions of the articular cartilages. In addition there were acute and chronic cellular infiltrations, hypertrophy of the synovia surrounding the joints and tendons productive of some tendonous adhesions, marked osteoelastic activity with periosteal osteogenesis, and some pannus formation in selected joints. Ankyloses, especially at the ankle and in the tail, were observed in some of the more chronic cases. Histologically these were formed by compact intra- and periarticular fibrous tissue. All other tissues were histologically negative, except for a granulomatous pneumonitis and an occasional small granuloma in the liver. Further experiments tended to show that the muscle may not be an essential constituent of the emulsion. Recently it has been noted that one subcutaneous injection into the dorsum of a single paw will produce reactions in another or all the remaining paws and in the tail in from 14 to 20 days.

Recently pleuropneumonia-like organisms of differing growth characteristics have been isolated from one of several joints in two of three animals so studied.

Discussion.—Dr. Marian W. Ropes (Boston, Mass.): I think this is a fascinating paper, particularly since I have been interested in the pleuro-pneumonia-like organisms in relation to joint disease. I should be particularly interested in the effect on the organism of antibiotics, especially terramycin. It is difficult to interpret a histological reaction in relation to the role of the organisms, since we know far too little about the histology and course of pleuropneumonia arthritis in most animals.

Dr. Pearson: I am pleased you asked that question, Dr. Ropes, as it gives me a chance to expand. I have used antibiotics, streptomycin, terramycin, and penicillin, and I have noted, in general, that when I give the adjuvant injection into the paw, there has been an intense reaction at the local site rather than a subsidence of the reaction. The reaction did not subside after a few days, or continue to be repressed, but the ultimate result of alteration in the peripheral joints was largely suppressed. A small degree of peripheral reaction occurred in a significant number of animals. For instance, a series of fifteen that received terramycin had intense local reaction in the paw, and five of these developed mild degrees of peripheral reddening of the joints. However, this peripheral reaction was only detected on day-to-day observation of the animals, and if they had not been examined for two or three days, this information would probably not have been available.

Dr. Walter Bauer (Boston, Mass.): These observations are of interest and are reminiscent of previous reports on experimental arthritis. It has been known for some time that Streptobacillus moniliformis is a common inhabitant of the lung of rats. The lesions produced by these organisms are readily demonstrated at autopsy. The small cavities are filled with dry, insufflated, yellowish material.

Dr. Hans Selye has reported the production of arthritis in rats by placing unilaterally nephrectomized animals on a high salt diet. He has also reported on modifications
of this manner of inducing arthritis in rats. In addition, he has described what one might term "formalin arthritis". Dr. Pearson now reports on a form of arthritis occurring in rats receiving injections.

Did the rats used by Dr. Pearson harbour either Streptobacillus moniliformis or pleuroneumonia organisms? If so, do we have to entertain the possibility that the injections represented an insult, or if you prefer stress and strain, of sufficient magnitude to permit the previously harboured organisms to become pathogenic and thereby cause the arthritis?

Pathology of the type demonstrated by Dr. Pearson can, of course, be produced by any number of agents; chemicals, toxins, and bacteria (particularly streptococci of low-grade valence). In some instances, the arthritis, though acute in nature, may be short-lived. In some instances, it may last no more than days or weeks. If the arthritis induced is more chronic in nature, it is more likely to resemble the histological features considered consistent with those of rheumatoid arthritis.

These and other factors must be taken into account if we are to evaluate correctly the experimental arthritis report by Dr. Pearson.

Dr. Pearson: I should like to add that, in complete autopsy surveys of these animals, they have not shown any other consistent systemic lesion. The lungs have been clear except for what I call a granulomatous pneumonitis. This is not an infrequent finding following the injection of adjuvants and may be a reaction to some of the oil. Also, an occasional, small fibrotic granuloma has been noted in the liver.

Dr. Bauer: Have you ever injected a normal rat joint with synovial fluid aspirated from an acutely involved joint?

Dr. Pearson: I have not.

Dr. Bauer: If a living agent is responsible for the experimental arthritis, this is an extremely important and relatively simple experiment which should be done.

Dr. Pearson: I have taken some of the viable pleuroneumonia organisms that Dr. Dienes has forwarded to me, cultured them on pleuroneumonia media, and injected the viable organisms into the paws and intra-peritoneally in rats. I have been able to obtain pure cultures from the paws. The animals have not developed any subsequent peri-arthritis.

However, in one series, I injected pleuroneumonia into the right paw and the adjuvant into the left paw. The pleuroneumonia reaction in the right paw subsided so that one could not tell that any injection had been given but in approximately two and a half weeks this area flared up again. This was probably a re-flare-up of the organism's activity, possibly under the stimulus of the action of the adjuvant which was present in the left paw.

Dr. John C. Nuneemaker (Arlington, Va.): Many years ago, when Dr. Brown and I did our work on rat bite fever, most of our rats were of the Wistar strain. Later I spent 6 years in Salt Lake City where all of the rats were of the Sprague-Dawley strain. In those 6 years I was never able to get the Streptobacillus out of that strain, and I would, therefore, suggest you extend your observations to the Sprague-Dawley strain.

Dr. Pearson: Stoeckl, Bielinski, and Budzilovich (1954) developed an arthritis which sounds very similar to mine. They injected Freund's adjuvant plus splenic extracts, and reported that antibiotics in large doses had no effect on this arthritis. They found no pleuro-pneumonia organisms.

Dr. Howard J. Weinberger (Beverly Hills, Calif.): If it is true that the pleuroneumonia-like organism represents an unusual growth form of hormone commonly occurring in bacteria, then almost any Gram-negative bacillus that may be indigenous in some organ in the animal may give rise to one of the pleuroneumonia-like organism strains, which could be arthrophytic and produce arthritis.

I should like to ask if Dr. Dienes did not attempt to reproduce the arthritis with the strain he recovered. The recovery of these organisms from the affected joints by Dr. Dienes and the attenuation or obliteration of the reaction with the antibiotics are strong evidences that the pleuroneumonia-like organism is responsible for the arthritis.

Dr. Pearson: I did not mention that because I am not certain of all the features. In the letter I received from Dr. Dienes he reported that he took some of these organisms and injected them into young rats and 5 or 8 days the animals died. They had arthritis. He did not tell me the route of injection nor the dosage, so I have not repeated the experiment. I am not certain exactly what he did, but he mentioned that organisms were isolated from a joint and from the area of the tail.

Dr. Joseph E. Warren (Pittsburgh, Pa): Some of these lesions resemble those seen in the rat treated with growth hormone. Since it is known that cessation of ovarian activity in the rat has a tendency to increase the growth hormone, I wonder if the author has any evidence as to what happened to the oestrous cycles in these animals.

Dr. Pearson: I am sorry that I do not know what happened to the oestrous cycle. I might say we originally considered growth hormone as a possible factor. The reports on growth hormone do not suggest that these lesions are very similar to those produced thereby. There is certainly an over-proliferation of bone in both of these diseases, but the inflammatory reaction does not seem to occur in animals infected with the growth hormone.

Dr. Jerome Rotstein (Minneapolis, Minn.): In view of Lawrence's recent article, have you done any cell transfer studies?

Dr. Pearson: I have not done any chemical studies on the cell. I should first like to clarify in my own mind the role of these pleuro-pneumonia-like organisms before progressing further.

REFERENCES


The vascular and articular lesions occurring in frostbite are typically focal and resemble those of acute rheumatic diseases; a common pathogenic factor may be impairment of local blood flow. In frostbite the problem of the pathogenesis of these lesions is particularly well suited to experimental investigation: the intensity of
injury may be controlled; the initiating physico-chemical changes are relatively mild; and most of the tissue damage appears to develop as the result of endogenous processes after the aetiological exposure to cold is terminated.

Frostbite was produced in the feet of more than fifty rabbits by exposing them to air at -25°C. Discrete vascular and articular lesions developed within 24 hrs of exposure and resembled those of acute rheumatic disease in the following characteristic histological features:

1. Localized necrosis.
2. Rapid fragmentation of emigrated neutrophils.
3. Deposition of amorphous fibrin-like material.
4. Alteration of collagen bundles.
5. Connective tissue hyperplasia.
6. Slow repair resulting in dense scarring.

The vascular lesions were most prominent in arteries. They were typically segmental but increased in size and number after more severe degrees of exposure. The joint lesions were localized to the articular margins where the cartilage was in contact with vascular synovial tissue. Arthritis developed only when freezing had been relatively brief and the synovial circulation had been partially restored. Neutrophil infiltration began 3 to 9 hrs after exposure to cold and preceded the resorption of cartilage. At this time arteriospasm had been released, but most of the blood was flowing through arterio-venous channels and circulation through the minute vessels was intermittent and sluggish.

Two pathogenic processes are postulated to account for the development of the articular lesions:

1. A primary cell injury representing an immediate effect of cold and resulting in leukotaxis.
2. A histolytic process responsible for the resorption of cartilage and connective tissue matrix.

The latter process appears to be mediated by poorly diffusible or corpuscular elements of the blood such as the neutrophils which tend to accumulate in the initially injured tissues during the period of sluggish circulation. A similar haematogenous factor may be concerned in the segmental necrosis of blood vessels.

Discussion.—Dr. John H. Vaughan (Richmond, Va): Did Dr. Kulka study the effect of heparin on the development of the histological picture in these lesions?

Dr. Kulka: No, we did not study the effect of heparin. It is one of the things we hope to do in the future.


Fibrinoid is a common feature in the lesions of the collagen diseases but haematoxylinophilia has been described as occurring only in disseminated lupus erythematosus. In turn, various investigators have postulated the origin of fibrinoid from either fibrin, degenerated collagen, or precipitated ground substance.

Morphological and tinctorial properties of fibrinoid derived from the following sources were studied: the diffuse collagen diseases; human and experimental hypersensitivity; and fibrinoid produced experimentally by various other means (mechanical, chemical, and physical). In all these instances the sequence of events showed the presence of fine strands of fibrin which later conglomerated to form masses showing all the characteristics of fibrinoid. These masses in turn showed the specific tinctorial properties of fibrin.

We were able to demonstrate that haematoxylinophilia and Feulgen positivity were properties of fibrinoid not only in disseminated lupus erythematosus but at times also in at least two other conditions: rheumatoid arthritis and polyarteritis nodosa.

Histochemically tyrosine, tryptophane, cystine, and cysteine were present in all the examples of fibrinoid studied. These amino acids were present in serum proteins but were absent or only present in low concentrations in collagen. Incubation of tissue with hyaluronidase altered the specific acid mucopolysaccharide staining material but not the fibrinoid. Trypsin resulted in the digestion of fibrinoid but not of collagen. Fibrinolysin led to the digestion of fibrinoid in frozen substituted tissue. These findings provide evidence for the almost certain origin of fibrinoid from fibrin.

Many of the mononuclear cells in the lesions studied were plasma cells in various phases of maturation. In serial time-studies of lesions of experimental hypersensitivity, plasma cells appeared in widespread fashion including the lesions typical of the collagen diseases.

Plasma cells are known to produce antibody. Their close association with the connective tissue lesions under consideration suggests that the latter are based on some aspect of local immune reaction. That they are not a response to connective tissue injury in evident because of their absence in association with fibrinoid produced by mechanical chemical or physical means. They are also absent in the passively-induced lesions of hypersensitivity.

These observations indicate the non-specific nature of fibrinoid as regards specific aetiology, but do point out the possible pathogenetic significance of the plasma cells as evidence of the hypersensitive nature of the "diffuse collagen diseases".

Discussion.—Dr. D. Murray Angervine (Madison, Wis.): About 10 years ago we gave a report on the nature of fibrinoid before this society, and it varied considerably from what Dr. More has said this morning.

I should like to congratulate him on his presentation and on the excellence and quality of the staining. I should also like to point out that in 10 years histochernistry made a good many advances.

There are two differences in our studies. I believe the fibrinoid we described was rather more mature; it had been present for a longer time and was better developed. As he showed to-day, in the development of early acute lesions, it looks like fibrin and is fibrin. This shows the importance of studying the earliest lesions from the pathogenetic standpoint.

I should like to ask one question. In the late, well-formed fibrinoid nodules, for example, in the vegetations in the heart valves of rheumatic fever, such lesions do not stain with fibrin stains. I wonder if he can explain where the transition stage takes place?
Dr. More: I think, in answer to the question posed by Dr. Angevine, I should start off from the first statement I made; that fibrinoid is an intensely eosinophilic or acido-philic material which is homogeneous and amorphous and possesses some of the tinctorial properties of fibrin. This is the only firm definition. It is not an exact physical chemical definition, but until the chemist has taken whatever we call fibrinoid and identified it as heterogeneous or homogeneous material chemically, we have no better way to define it.

In regard to the tinctorial properties of the material in the centre of old rheumatoid nodules, I would ask whether the material that Dr. Angevine has referred to is merely homogeneous and eosinophilic, or whether it is homogeneous and intensely eosinophilic? If it is the latter I believe it will possess the tinctorial properties of fibrin.

Some of the lesions we produced experimentally, first seemed to be homogeneous, but on careful study the borders were seen to be intensely eosinophilic, whereas the central parts were not so eosinophilic. The central parts do not stain with fibrin stains, whereas the peripheral portions do so.

It is our impression that this homogeneous, pink material is derived from blood plasma constituents, including fibrin, and that it is the fibrin component of the material that goes on to produce fibrinoid, whereas the other material may appear homogeneous and eosinophilic but without possessing all the tinctorial properties of fibrin proper.

Dr. Jerome Gross (Boston, Mass.): It may very well prove true that fibrin is an important component of fibrinoid, but with regard to the histochemical demonstrations, I think the conclusiveness of identification, in spite of the advances that Dr. Angevine has mentioned, is still not clearly established. Nor are these staining reactions numerous enough to allow reliable comparison.

It is interesting that you should say that the background of connective tissue and the cells give no positive Millon reaction for tyrosine, or Barnett reaction for sulphur-containing amino acid. The connective tissue has plenty of blood protein, and the cells are not collagenous and have plenty of tyrosine and sulphur-containing amino acids, which should also take the stain.

There may be a quantitative difference, but this does not consist in a difference in the type of protein present. For example, the compactness of material you show might be the cause of the intense staining. It could be the same stuff as is present in ground substance, but might differ in staining because of a greater density of substance. Perhaps, even in the cutting, you have a larger thickness of material which might be the same as in the normal connective tissue, but with different physical properties. All these things can give rise to difference in staining.

From my own experience, I know of some forms of collagen which, when stained with Mallory's connective tissue stain, will stain red while other forms will stain blue, yet they are all collagen.

Dr. More: I think the questions raised by Dr. Gross are those we are aware of. The failure to demonstrate material with the tinctorial properties of fibrin in normal connective tissue does not rule it out. The condensation of such hypothetical substance into visibly demonstrable fibrinoid during pathological alteration must be considered. However, in view of the presence of increased amounts of the normal constituents of connective tissue without the presence of fibrinoid on the one hand, and the presence of fibrinoid unassociated with increased amounts of the normal components of connective tissue on the other, it is doubtful whether condensation of the materials normally present in connective tissue would lead to the formation of fibrinoid. We are inclined to believe that there may be in pathological states an increase or swelling of the connective tissue components, as one manifestation of injury or repair, and in addition there may be exudation of foreign material which takes on the properties of fibrinoid.

Dr. More: I am sure that when this work is published statements regarding fibrinoid will be phrased in such words.

Dr. J. P. Kulka (Boston, Mass.): We have been interested in the same problem for some years and have arrived at almost identical conclusions.

The fibrin-like material in rheumatic lesions resembles the exudate of fibrinous pericarditis and the mural thrombi lining arterial aneurysms. It differs, however, from the delicate reticular form of fibrin which is characteristic of lobar pneumonia and other acute pyogenic processes; it is more compact, more resistant to resolution, and more likely to undergo slow organization. These properties of the fibrin-like material in lesions of rheumatic diseases are of interest because they may well be a factor in the tendency of such lesions to cause adhesion formation, to heal slowly, and to result in dense hyalin scars.

Dr. More: There is no doubt that a physiochemical change is produced. It does not have all the properties of fibrin, but it has some of them and that is why it has been likened to fibrin. What this physiochemical change means I do not know, except in regard to the one question that Dr. Kulka raises: it does not follow the same course as fibrin in terms of organization.

Dr. Walter Bauer (Boston, Mass.): Would it be more correct to conclude that there is a distinct possibility that fibrinoid arises from fibrin?

Purification of the Accessory Agglutinating Factor of the Serum in Rheumatoid Arthritis. By Joseph Lospalluto and Morris Ziff, New York, N. Y.

With the objective of isolating the sheep cell agglutinating factor, serum from patients with rheumatoid arthritis was fractionated by a number of methods.

On precipitation with ammonium sulphate, the agglutinating factor was obtained at concentrations of salt between 1:2 and 1:4 molar. This fraction yielded an active euglobulin when dialysed at pH 7. Treatment of this euglobulin by cold globulin precipitation yielded a fraction which contained all of the agglutinating activity of the original serum in 1:6 per cent. of the original nitrogen, a purification of about 60-fold. Electrophoresis of this product indicated the presence of at least two components with mobilities in the gamma- and beta-globulin range. The presence of inhibitor of sensitized sheep cell agglutination was demonstrable in rheumatoid as well as non-rheumatoid sera in globulin fractions precipitating at concentrations of ammonium sulphate higher than 1:4 M.

More complete purification of the agglutinating factor was achieved through the use of ion exchange chromatography. It was possible to obtain fractions purified...
more than 500-fold over the original serum. Electrophoresis of a fraction prepared in this way showed the presence of two components with mobilities in the gamma-globulin range.

A number of properties of the agglutinating factor were studied. In experiments performed on the euglobulin fraction obtained by dialysis of rheumatoid serum at pH 7, complete loss of activity occurred at 100°C after 30 min; part of the activity remained after 30 min at 78°C. The factor appeared to be stable over the pH range 4 to 11. Above and below these limits there was complete loss of activity. Enzymatic treatment of the euglobulin with trypsin or papain appeared to have no effect on its activity; little evidence of proteolysis was demonstrable.

Though the agglutinating factor occurs almost specifically in the serum of patients with rheumatoid arthritis, the inhibitor appears to be present in all human sera. In contrast to the agglutinating factor, inhibitor activity could not be concentrated in any single globulin fraction, but was precipitated over a wide range of salt and hydrogen ion concentration. It did not appear from the chromatographic data that the inhibitor was present in sufficient amounts to modify the agglutination titre of rheumatoid sera.

A Precipitin Reaction between Human Gamma Globulin and the Serum of Patients with Rheumatoid Arthritis.

By WALLACE EPSTEIN, ALAN M. JOHNSON, and CHARLES RAGAN, New York, N. Y.

It has been established that the various serological tests used for the diagnosis of rheumatoid arthritis have a certain degree of specificity, and extensive investigations have been conducted in an effort to purify and characterize the "rheumatoid factor" present in a positive serum. These efforts have been hampered by the need for a sheep cell indicator system to detect its presence.

One of the sheep cell agglutination tests used is the gamma globulin (Fraction II) test which involves coating tannic-acid-treated sheep red cells with pooled human gamma globulin and suspending these cells in various dilutions of the patient's serum.

Current studies have revealed precipitate formation when pooled human gamma globulin is combined with the serum of patients having rheumatoid arthritis and a positive Fraction II test in the absence of sheep cells.

Dilution studies revealed characteristics of an antigen-antibody system between some constituents of pooled human gamma globulin functioning as an antigen and the rheumatoid factor as an antibody. By the quantitative precipitin technique, the relative weights of gamma globulin antigen and precipitate formation suggested that the antigen constitutes only a small fragment of the total gamma globulin. Precipitin curves suggested at least one interacting system using commercial liquid gamma globulin and at least two such precipitin systems using commercial powdered Fraction II.

In sera of patients having Fraction II titres of 7,000 to >56,000, 89 per cent. produced precipitates when commercial liquid gamma globulin was used, 100 per cent. when powdered Fraction II was used 61 per cent. revealed spontaneous precipitates in the cold which did not redissolve on heating.

Discussion.—DR. JOHN H. VAUGHAN (Richmond, Va): Dr. Epstein and his fellow-workers have certainly presented us with a very exciting new finding.

A year ago I had the pleasure of reporting to this group that the sensitized sheep cell factor can be absorbed by antigen-antibody precipitates prepared from rabbit immune sera. This was shown both by a reduction or disappearance of sensitized sheep cell activity after absorption of the serum by the precipitates and by the addition of protein nitrogen to the precipitates. When we first heard of Dr. Epstein's new finding, we were naturally interested to know how the material precipitable with Fraction II might be related to the material absorbable by rabbit immune precipitates. Correspondingly, four rheumatoid sera of various titres of sensitized sheep cell agglutinating activity were absorbed with egg-albumen anti-egg albumen rabbit immune precipitates. We then compared the amount of nitrogen precipitable by given quantities of Fraction II from aliquots of the absorbed and unabsorbed sera. A marked reduction in the amount of precipitate was noted in the absorbed serum, indicating a definite relationship between the materials measured by these two techniques. It was significant to note, however, that the absorption with rabbit immune precipitate did not remove all material precipitable by Cohn Fraction II. These results are consistent with the presumption that the rheumatoid factor is an antibody having primary specificity to a normal component of human serum and cross-reacting with a component in rabbit serum.

It was of further interest to us to note that the amount of precipitate obtainable on addition of Fraction II to a rheumatoid serum is dependent upon the amount of dilution of the rheumatoid serum effected. Thus, when a quantity of Fraction II is added to a given rheumatoid serum in such concentration as to effect only a 4:5 dilution of the rheumatoid serum, little or no precipitate may be seen. However, when the same amount of Fraction II is added to the same amount of rheumatoid serum in a volume such as to provide a 1:5, 1:10, 1:20, or 1:40 dilution of the rheumatoid serum, an increasing amount of precipitate is formed, the curve plateauing at about 1:20. On analysing the supernatants, it was noted that one could detect neutralization of the rheumatoid factor without having the precipitates fully formed. Such discrepancy thus seen between agglutination end points and points of maximum precipitation may be of importance in interpreting the studies Dr. Epstein has just described to us. They indicate that caution must be taken in deciding whether or not we are dealing with two completely independent systems, as has been suggested, or whether we are dealing with a single system.

DR. EDWARD E. FISCHEL (New York, N. Y.): Does the rheumatoid serum spontaneously precipitate in the cold? What was the level of nitrogen in the blanks during the quantitative precipitin reactions? Was there a large amount of nitrogen or was it the usual trace amount?

DR. EPSTEIN: The sera used for quantitative precipitin studies were first centrifuged under refrigeration until no further spontaneous precipitate formation could be detected.

Quantitative measurements of the amount of spontaneous precipitate formed showed wide variations from
day to day in the same individual. Blood was allowed to clot at 37° C. for these studies.

**Latex-Fixation Test in Rheumatoid Arthritis. By**

**CHARLES M. PLOTZ and JACQUES SINGER, New York, N.Y.**

One difficulty with the previously described serological tests for rheumatoid arthritis has been the introduction of extraneous biological properties related to the particles to be agglutinated (sheep erythrocytes, streptococci, etc.). Polystyrene latex particles have been found by us to be suited to serological technique. In simple test these commercially obtainable particles were mixed with commercial gamma globulin and added to progressive dilutions of sera from patients with rheumatoid arthritis and a typical agglutination reaction occurred. The test can be done easily and in quantity in a single morning.

1,200 patients were tested by this carrier mechanism to which we have applied the name latex-fixation. 100 patients with the submitted clinical diagnosis of rheumatoid arthritis were tested by the latex-fixation method, the Rose-Ragan method, and the Fraction II technique of Heller. Positive percentage was almost identical: 12 patients negative to the Rose-Ragan test were positive by latex-fixation and four patients with 1:64 Rose-Ragan titres were negative to latex-fixation. With the latex-fixation test the doubtful group was eliminated, since either a strong positive or a negative was obtained. The overall incidence of false positive latex-fixation tests was less than 2 per cent., comparable to the other methods.

Various properties of latex particles, such as behaviour with various electrolytes and varying pH, and the use of the latex-fixation technique in other serological systems have been studied. The effect of the size of the particles, concentration of particles and antigen, temperature, shaking, centrifugation, and pH were studied.

The results indicate a rapid, technically easy, and reliable new test for rheumatoid arthritis. The carrier technique of latex-fixation has the experimental advantage of limiting the biologically active factors to gamma globulin and the serum being tested. The findings suggest the possibility that the nature of the agglutinating factor in the serum of patients with rheumatoid arthritis may be an auto-antibody against a gamma globulin.

**Discussion.—Dr. Morris Ziff (New York, N.Y.):** This is an intelligent approach to a method which gets us away from the infernal red cell and the necessity for inactivation of complement, and which avoids the tedious absorption of sera.

I suspect, from a practical point of view, that, in the long run, for diagnostic purposes we shall probably have to rely on some sort of agglutination test rather than on a precipitin test, since agglutination tests are, in general, more sensitive than precipitin tests.

I have analysed the relationships involved in the various tests described here at this meeting and at last year’s meeting.

In the usual test, the red blood cell is sensitized with rabbit antibody or gamma globulin in the form of amboceptor. The sensitized cell, then, has the opportunity to react with the rheumatoid factor, presumably by virtue of combination between the rheumatoid factor and the rabbit antibody coating the red cell. When inhibition is carried out by addition to such a system of human euglobulin, the rheumatoid factor has two possibilities for reaction: it can attach itself to the red cell and if this occurs, agglutination takes place. In the presence of excess of human gamma globulin, however, the reaction is probably forced by mass action towards a combination between the gamma globulin and the rheumatoid factor. The latter is then not left to react with the sensitized sheep cell and agglutination is inhibited.

The properties of tannic-acid-treated cells are apparently so altered that they can be more easily coated with proteins. In the Fraction II test, one has a sheep red cell which is coated with human gamma globulin, just as in the old tests the sheep red cell was coated by rabbit gamma globulin. The same sort of reaction takes place, in that the rheumatoid factor reacts with the coated red cell and agglutination occurs, this time on the basis of reaction with a gamma globulin coating which happens to be human rather than rabbit.

In the test just described by Drs. Plotz and Singer, one deals with latex particles instead of with the tannic-acid treated cell. This latex particle can apparently be coated when exposed to human gamma globulin, and can then react, by virtue of this coating, with the rheumatoid factors. As a result, the latex particle agglutinates. It has been shown that this reaction between the rheumatoid factor and gamma globulin can be demonstrated in a particle-free system in which the rheumatoid factor precipitates with human gamma globulin. In all cases it would seem as though the essential reaction involved is one in which the rheumatoid factor reacts with a constituent of the gamma globulin, whether human, rabbit, or otherwise.

**Dr. Grace P. Kerby (Durham, N.C.):** I believe this technique is going to be of particular use in investigating some of the problems related to rheumatoid agglutination tests.

Our only experience in trying to substitute inert particles for the sheep cell was the use of ionic exchange resin particles, but we did not pursue this to the successful conclusion that Dr. Plotz has presented.

Our major experience has been with the more usual sheep cell technique, and we have varied only in that we have substituted Neurath’s method of rapid mineral acid precipitation of the globulin fraction for the overnight dialysis technique. We have found that the preliminary absorption of serum is not necessary usually, appropriate controls being included to detect the occasional exception. With this technique we have had about the same results as are reported from other laboratories, i.e. about 85 per cent. positive in clinically unequivocal rheumatoids, and about 83 per cent. negative in all other patients with or without joint diseases.

As regards the specificity of these two techniques, it would seem that the sheep cell technique gives a somewhat larger percentage of positives in the clinically unequivocal rheumatoid group.

I noticed Dr. Plotz had one positive out of twenty patients with lupus erythematosus. Our experience has been that about half of these patients are positive. From that point of view, it would seem his technique has proved more specific than the cell technique. I wonder if some of the difference may be due to the difference between using euglobulin fraction and using whole serum. I should be interested to hear any data on the use of the euglobulin fraction in the latex system.
I should be interested to hear what portion of the commercial gamma globulin fraction is the most active in the latex test, this because of the recent reports of the role of the basic fractions of gamma globulin in the flocculation tests. From our own quite preliminary observation in this direction, I suggest that in the rheumatoid tests as in flocculation tests, the more basic fractions of gamma globulin may prove to be the more active.

DR. JOHN H. VAUGHAN (Richmond, Va): I think it is important to take issue with one point raised in this discussion, and that is whether or not we are dealing with cells coated just with gamma globulin. I think it should be noted that this is gamma globulin on the cells plus the impurities in the gamma globulin preparation used to coat the cell. If you go back to some tanned cell studies which have been done with a much more purified protein than gamma globulin (i.e. crystalline egg albumen), it has been demonstrated by Dr. Stavitsky at Western Reserve University that components of egg white other than egg albumen can be responsible for the agglutination reaction of cells coated with crystalline egg albumen. So, I think one should always say very clearly that these cells are coated with gamma globulin, plus the impurities that were in the gamma globulin preparation.

Secondly, in terms of sheep cells coated with rabbit antibodies, we must again visualize that other substances besides the antibody may be in the cell coating. Components of serum complement may be present, as well as other more stable serum components. It can be shown, for instance, that when an Rh-positive red cell is particularly highly sensitized with anti-Rh antibody, the coated cell will apparently non-specifically absorb serum proteins other than complement.

Thus irrespective of the mode of coating cells for demonstrating the rheumatoid factor, it is necessary to remember that we have not yet attained a system that can be shown to give a single, well-defined coating material.

DR. PLOTZ: Commercially prepared gamma globulin is certainly an impure substance. I should like to reiterate that we have a number of presumably pure fractions that we are now trying to work with.

Also, I should like to make another point that I did make briefly in the paper: that the particles in about 80 per cent. of positives may be precipitated in the absence of gamma globulin.

Metabolic Effects of Aspirin Therapy in Rheumatoid Arthritis. By DANIEL M. BACHMAN, EVAN CALKINS, and WALTER BAUER, Boston, Mass.

Acetylsalicylic acid (aspirin), when administered in proper therapeutic dosage, remains the most efficacious drug in the long-term treatment of patients with rheumatoid arthritis; however, little is known concerning its metabolic effects in this disease. The present study was undertaken in order to survey some metabolic responses of patients with rheumatoid arthritis to therapeutic doses of aspirin.

Five patients with active rheumatoid arthritis were studied during control period and during periods when they received aspirin in daily doses of 3-3 to 6 g. Joint swelling, pain, and stiffness diminished during aspirin therapy and returned when aspirin was discontinued. Metabolic balance studies were performed on all patients. Investigation of acid-base balance included concurrent measurements of ventilation, urinary excretion of acid and of serum pH, and total CO₂ content.

Moderate doses of aspirin did not produce changes in the metabolic balances of nitrogen, sodium, potassium, calcium, phosphorus, or magnesium. Higher doses, accompanied by mild symptoms of toxicity, resulted in increased urinary excretion of nitrogen and phosphorus and in less positive nitrogen balances. Therapeutic doses of aspirin resulted in the following average changes:

- Increased basal minute volume of ventilation (3 l./min.).
- Decreased alveolar CO₂ tension (10 mm. Hg).
- Increased B.M.R. (30 per cent. above control).
- Decreased serum CO₂ content (8 mEq./l.).
- Increased serum chloride (8 mEq./l.).
- Decreased, increased, or unchanged serum pH.
- Urinary excretion of ammonium increased (20 mEq./24 hours).
- Urinary titratable acid increased (15 mEq./24 hours).
- Urinary excretion of 17-OH corticosteroids or 17-ketosteroids unchanged.

Discussion.—DR. CHARLES M. PLOTZ (New York, N.Y.): Did you use any salicylates other than aspirin in your study?

DR. BACHMAN: This study was primarily concerned with the action of aspirin, but we have also compared the action of acetylsalicylic acid and sodium salicylate in the same patient. This patient was receiving a therapeutic dose of aspirin for several days before the beginning of the study and had a plasma salicylate level of 20 mg. per cent. at the beginning of the study. The patient was studied for 7 days during which she received aspirin, 8 days during which she received no medication, and 6 days during which she received sodium salicylate in chemically equivalent dosage. The actions of aspirins and sodium salicylate were similar, in that both produced increases in the minute volume of ventilation, decreases in total plasma CO₂ content, and slight rises in serum pH. The striking difference between the two compounds as shown by this particular study was the fact that aspirin therapy was accompanied by an increase in the urinary excretion of acid, whereas sodium salicylate therapy was accompanied by an initial transient fall in urinary acid excretion followed by a return to the control level. The patient was receiving a constant diet throughout the course of the study.

DR. PEARSON: You have talked primarily about patients with rheumatoid disease. Do you expect that normal people would react in the same way to aspirin as to the other salicylates?

DR. BACHMAN: There are a few studies in the literature pertaining to the effects of salicylates in normal individuals. Dr. J. H. Means, Emeritus Professor of Medicine at the Massachusetts General Hospital, studied the effect of salicylates upon basal metabolic rates of normal individuals as early as 1916. One of the most recent studies of the respiratory effects of the salicylates in normal individuals appears in a paper by Tenney and Miller (1955). They found effects upon respiration and...
oxygen consumption similar to those seen in our patients with rheumatoid arthritis.

**D.R. Richard H. Freyberg (New York, N.Y.):** It was interesting to hear these important data concerning the metabolic effects of acetylsalicylic acid.

Was there any significant difference between the various female patients? or were there any differences between the sexes?

**D.R. Bachman:** There were four female patients and only one male, so perhaps we should not conclude too much about sex differences. The data presented today were typical of the results in all five patients. It happened that some of these changes were of smaller magnitude in the male patient. I think this may have been due to the fact that the male patient received a smaller dose of salicylate in proportion to his body weight than did the female patients.

**D.R. Otto Steinbrocker (New York, N.Y.):** Did you observe any correlation of the symptom response with the physiological or chemical reactions that occurred?

**D.R. Bachman:** These patients all seemed to fare better when they were taking aspirin, in terms of obtaining relief from joint pain and stiffness, and often, subsidence of joint swelling. When we discontinued the aspirin, there was a return not only of pain and stiffness but, in several cases, of joint swelling and heat. We are unable to say anything at present about a possible correlation between the clinical state of the patient and the observed physiological findings.

**D.R. Roland Davison (San Francisco, Calif.):** What did the figures for 17-ketosteroids and corticocoids show?

**D.R. Bachman:** We did not determine these in all patients. The data obtained thus far show no significant change in the urinary excretion of either 17-hydroxy-corticosteroids or 17-ketosteroids.

**D.R. John C. Seed (Scarsdale, N.Y.):** I should like to comment on the two most important factors influencing minute volume: oxygen consumption and responsiveness of the respiratory centre to carbon dioxide.

Any increase or decrease in oxygen consumption will cause a corresponding increase or decrease in carbon dioxide production. With a change in carbon dioxide production minute volume must change accordingly if homeostasis is to be maintained. Minute volume times carbon dioxide concentration in the expired air equals carbon dioxide excretion, and excretion must equal production for homeostasis. Indeed, excretion must equal production at all times, except for short periods of change from one set of equilibrium conditions to another.

With regard to the response of the respiratory center to carbon dioxide, any factor such as aspirin which causes an increased response will cause an increase in minute volume, at the expense of homeostasis. In Dr. Bachman's work it would seem that both factors are active.

I wonder whether Dr. Bachman had any further comment upon the interrelationship between oxygen consumption and response of the respiratory center or whether he has any idea why aspirin increases the metabolic rate.

**D.R. Bachman:** You have drawn attention to a problem which is very difficult to answer: whether the increase in minute volume which we observed when the patients were in the basal state was due to acid-base adjustment, to a primary stimulating effect of salicylate on the respiratory center, or to an increase in basal metabolism. At present, we are unable to say how much each factor contributed to the observed increases in basal minute volume. Neither can we conclude whether the changes in B.M.R. were primary or secondary to the respiratory changes. Tenney and Miller (1955) reported increased oxygen consumption in dogs given salicylates, and in the eviscerated animal, and in the curarized animal ventilated in a whole-body respirator. These workers have postulated that one site of action of salicylate might be the skeletal muscle.

**Reference**


**Differential Diagnosis of Ankylosing Spondylitis. By James Sharp, Manchester, England.**

In approximately one-fifth of the patients attending a special spondylitis clinic, the clinical picture differed in various ways from that of classical ankylosing spondylitis, although most of them had bilateral radiographic changes in the sacro-iliac joints.

Analysis of the results of deep x-ray therapy revealed that those with straightforward ankylosing spondylitis were mostly much improved after this, but that the majority of the "atypical" cases were unimproved. These results could not be ascribed to longer duration of symptoms or to a preponderance of unusually severe cases in the atypical group.

As the effect of x rays appeared to be a local effect on irradiated tissues, these findings suggested that patients with "atypical" spondylitis might be suffering from other diseases resembling ankylosing spondylitis clinically but unresponsive to x rays. Some patients had psoriasis, and others had features suggesting rheumatoid arthritis, recurrent rheumatic fever, or Reiter's disease with specific involvement.

A study of other patients with these conditions revealed features by which they can usually be distinguished from ankylosing spondylitis. On review, approximately half of the atypical cases from the spondylitis clinic appeared to fit into the above categories. In some of the remainder, the spinal changes appeared to be due to osteo-arthritis, two had radiographic changes of "senile ankylosing hyperostosis", and two others had a hereda-familial form of spondylitis associated with calcinosis of limb joints and blood vessels. In a few patients the diagnosis remained obscure.

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**Four Papers Presented in conjunction with the American Council on Rheumatic Fever and Congenital Heart Disease**


The inoculation of Group-A streptococcal cultures intradermally in rabbits was found to elicit the appear-
stance in the serum of complement-fixing antibodies to normal rabbit-heart tissue suspensions. Antibody titres reached a peak within 2 weeks after the inoculation and rarely persisted longer than 3 to 4 weeks. Repeated monthly injections for 1 year with small doses of streptococcal cultures of the same type or of successively different types, by either the intradermal or intravenous route, resulted in each case with a rapid rise and fall of antibody after each injection, and only rarely in a sustained elevated level. Heat-killed cultures also evoked antibody responses, which frequently were more marked than those evoked by live cultures. Culture filtrates or beef-heart medium alone were usually ineffective, but small transient rises were produced in a few animals. When the experiments were carried out with streptococci grown in a medium derived from a digest of casein and soy bean (tryptase-soy broth), antibodies to heart tissue were not found.

These results suggested that the active antigen eliciting the production of antibodies reactive with rabbit heart is a hapten with organ specific properties present in the beef-heart medium and absorbed by bacterial cells during growth. This interpretation is also supported by the observation that immunization of rabbits with beef-heart tissue suspensions has also evoked such complement fixing antibodies to rabbit-heart tissue. Chemical studies have thus far identified the substance in rabbit-heart tissue and in beef-heart medium as alcohol and ether soluble, precipitable by barium salts and presumably associated with a proteolipid. Immuno-histochemical identification of the antigen in rabbit-heart sections by a modified fluorescent antibody technique has revealed it within the sarcoplasm of the myocardial cell adjacent to the cell membrane and between the myofibrils, showing a distribution similar in some respects to that of myocardial cell lipid as detected by Sudan black or phosphine 3 R stains.

Discussion.—Dr. Currier McCWen (New York, N. Y.): Did you use only haemolytic streptococci of Group A?

Dr. Kaplan: We carried out our experiments with Group A of the various groups. We also carried out some control experiments with Streptococcus viridans, with which no antibodies to the heart were found. We did not use any groups other than Group A.

Dr. W. K. Ishmael (Oklahoma City, Okla.): Have you had an opportunity of observing the beta-haemolytic streptococcus isolated from glomerulonephritis patients, with similar studies on the kidney?

Dr. Kaplan: We have not really carried out any detailed studies of this kind. Of course, we have used Type-12 strains. They show complement-fixing bodies to the heart. I am afraid we have nothing to say about work with the kidney.


This test is for sialic acid (SiA test). The normal range of values for 85 children and adults in good health is 0-227 to 0-303. The range of values for three diseases studied was:

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<tbody>
<tr>
<td>Acute rheumatic fever . . .</td>
<td>37</td>
<td>0-372 to 0-592</td>
</tr>
<tr>
<td>Tuberculosis (different stages)</td>
<td>11</td>
<td>0-292 to 0-665</td>
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<tr>
<td>Cancer (different stages) . . .</td>
<td>6</td>
<td>0-332 to 0-590</td>
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The test involves the use of only three materials:

1. 10 per cent. trichloracetic acid.
2. Glacial acetic acid.
3. Concentrated sulphuric acid.

In comparison with results obtained on diphenylnamine determinations from 68 consecutive rheumatic patients we obtained the following:

(a) Agreement. —D. P. A. positive, sialic acid positive 178 out of 318.
(b) Agreement. —D. P. A. negative, sialic acid negative, 95 out of 318.
(c) Disagreement. —D. P. A. positive, sialic acid negative, 2 out of 318.
(d) Disagreement. —D. P. A. negative, sialic acid positive, 41 out of 318.

Serial determinations showed that the SiA test, compared with the erythrocyte sedimentation rate (Wintrobe) appeared to be a more sensitive expression of persistent rheumatic inflammation. The return to normal values in eighteen patients studied was slower in twelve and coincidental in five, but in one case the erythrocyte sedimentation rate followed that of SiA. The average difference in return to normal values was 2 weeks slower for the SiA test.

The SiA test is easy to perform, gives reproducible results, and reflects minimal inflammation.


Electrophoretic fractions of sera show quantitative changes in the course of acute rheumatic fever and active rheumatoid arthritis. Elevations of alpha- beta- and gamma-globulins are observed in both conditions; in rheumatoid disease the albumin fraction is frequently decreased. These changes revert toward normal spontaneous remissions or successful response to treatment. Serum polysaccharides, as determined by several methods, increase in the course of these illnesses and decrease as inflammatory activity subsides. The purpose of the present investigation was to study polysaccharides of serum fractions separated by the method of paper electrophoresis. In order better to characterize mucoproteins, electrophoresis of sera was carried out both at pH 4.5 and 8.6. Analyses were run in triplicate so that migrated fractions on each sheet of paper could be stained separately with the following reagents:

(a) bromphenol blue,
(b) basic fuchsin,
(c) toluidine blue.
Separate visualization of serum protein fractions was possible after the application of bromphenol blue. Polysaccharide components were visualized with basic fuchsin if they contained “1,2 glycol” groupings which were oxidizable to aldehydes, or with toluidine blue if they were capable of being stained metachromatically. When electrophoresis of sera was carried out at pH 8-6, protein-bound polysaccharides associated with the alphaglobulins were most generally increased in blood from persons with active disease, and they returned to normal as activity subsided. Mucoproteins separated electrophoretically at pH 4-5 also paralleled the degree of disease activity. This was observed in both M-1 and M-2 components. There were no significant differences between the stained patterns of sera from patients with acute rheumatic fever and those of sera from persons with active inflammatory rheumatoid arthritis. In patients with rheumatoid arthritis no consistent parallelism was found between sheep cell agglutination titres and amounts of polysaccharide, since sheep cell titres remained significantly high even after successful response to treatment and a return to normal of the electrophoretic components.

Discussion.—Dr. John H. Vaughan (Richmond, Va): Have you studied any other generalized diseases that do not involve the connective tissue which might have an increased sedimentation rate, such as hepatitis or generalized carcinoma, and would these also provide the elevated serum polysaccharides?

It might be worth pointing out that when one has a large amount of gamma-globulin in a serum, particular pains are necessary to determine whether a higher betaglobulin peak represents anything other than more gamma-globulin, inasmuch as it has been demonstrated from immuno-electrophoresis that gamma-globulin can have the mobility of beta-globulin.

Dr. Kuhns: This test (periodic acid-Schiff stain) does not necessarily differentiate between various diseases on the basis of abnormalities in serum polysaccharides. In this sense, the test is non-specific, as are other tests for inflammatory activity. We have examined serum from patients with liver disease and with malignancy, and they have shown stained electrophoretic patterns which are very similar to those seen in inflammatory states such as rheumatoid arthritis.

Dr. Jerome Rotstein (Minneapolis, Minn.): Is there any chronological sequence in the amounts of polysaccharide that arise, as in Ropes’ work where they showed the beta-globulin followed by gamma-globulin?

Dr. Kuhns: Do you mean proteins or polysaccharides?

Dr. Rotstein: Is there any chronological relationship between the globulin and polysaccharide elevations?

Dr. Kuhns: It has been asked whether abnormal changes in serum proteins and polysaccharides were parallel as indicated by the respective stains, or whether there was any evidence of divergence between the protein and polysaccharide content of a fraction with changes in disease. In our experience, the bromphenol blue and the periodic acid-Schiff stains reflected similar proportional changes in the same serum globulins during the course of rheumatoid arthritis.

Dr. William K. Ishmael (Oklahoma City, Okla) I think there is a definite relationship between inflammatory activity and elevation of the protein-bound polysaccharide. We found, in gravitating the inflammatory reaction, that it is better to express serum polysaccharide in relation to serum protein (polysaccharide-protein ratio). This gives you a more significant correlation coefficient with the inflammatory reaction.

Dr. Kuhns: Is this the tryptophane?

Dr. Ishmael: Yes, the Shetlar method.

Dr. Kuhns: The matter of defining the method employed was taken into consideration, since there are several indices, those used for estimating the nucleo-proteins such as tyrosine content or total protein content.

Dr. Ishmael: We are preparing our material for publication on paper electrophoresis analysis of glycoprotein fractions. This data grossly correlates well with the chemical method and does indeed have considerable promise.

Dr. Kuhns: I am sure, for instance, in comparing the starch method, to estimate tyrosine and tryptophane, there was a difference in the amount of material observed as compared with the amount of Schiff staining material in corresponding serum. So defining the method is important.

Dr. Eugene L. Hess (Chicago, Ill.): I am a member of the Rheumatic Fever Institute and a co-author of the preceding paper. I wish to correlate the two papers, in that the paper presented by Dr. Kuhns demonstrates, I think, very well, the rise in the poly-saccharide-containing components in serum. It is well established that in almost any type of inflammation this rise is a commonly observed phenomenon. This has been shown by moving boundary electrophoresis by chemical methods, and very well by Dr. Kuhns.

It has also been quite well established that sialic acid is a common constituent of the mucoproteins present in the alpha-globulin fraction of serum. The test described by Dr. Coburn in the preceding paper appears to be specific for sialic acid, and therefore for mucoproteins.

The method described by Coburn is a variation of an earlier colorimetric method employing diphenylamine reagent. Anderson and MacLagan (1955) in England have stated that the diphenylamine test appears to be specific for mucoproteins.

I think that it is interesting to note that the methods described in these two papers measure essentially the same thing, the rise in mucoprotein levels in serum during inflammation: one by a physical technique and the other by a chemical technique.

Dr. Melvin H. Kaplan (Boston, Mass.): Did Dr. Kuhns carry out any lipid stains in association with the M-1 and M-2 spots?

Dr. Kuhns: We have already carried out lipid stains and we have studied electrophoretic serum fractions from patients with rheumatoid arthritis using Sudan black stain, but there seems to be no correlation between the amount of stained material and clinical status. However, there is evidence that Sudan black does not give a true picture of the lipid material contained in serum (Davis, 1955). This subject requires further investigation.

Dr. Grace P. Kerby (Durham, N.C.): Dr. Kuhns mentioned using toluidine blue stain on the electrophoresis strips to demonstrate certain polysaccharides in serum, and one presumes that this was for checking on the presence of mucopolysaccharides. It seems quite clear now that mucopolysaccharide-like substances are
present in serum, apparently closely associated with certain globulin fractions, as reported by Badin, Schubert, and Vouras (1955), and by Schiller and Dewey (1956). Our own experience confirms this in the course of studying these materials in plasma. However, it has been our experience that the toluidine blue stain will not satisfactorily demonstrate the metachromasia of these substances while they are still associated with proteins. If separated and concentrated for electrophoresis in a form suitable for later toluidine blue staining, the factors used for electrophoresis in the present study would probably not have been suitable for these fast-moving components.

I wonder if Dr. Kuhns has any further studies on these polysaccharide fractions in the serum he has studied.

**DR. KUHNS:** We reported that electrophoretic patterns treated with toluidine blue gave uniformly negative results in regard to the ability of fractions to be stained metachromatically. Dr. Kerby has asked if our negative results with the toluidine blue stain might have been due to the inability of this stain to produce metachromasia in protein-bound polysaccharides as they occur in the major electrophoretic fractions. We have not as yet carried out further work with toluidine blue, but as she has suggested, split products (obtained, for example, by hydrolysis) processes from zone electrophoresis eluates might be worthy of additional studies in this respect.

**REFERENCES**


(4) Mass Penicillin Prophylaxis in the Control of Civilian Streptococcal Epidemics. By DAVID C. POSKANZER, Albany, N.Y., HARRY A. FELDMAN, and WILLIAM G. BEADENKOFF, Syracuse, N.Y.

The occurrence of acute streptococcal epidemics among students attending central schools in two upstate New York communities presented us with unusual opportunities to study their epidemiology and to evaluate two different methods for their control. Although a number of mass prophylaxis experiments have been reported from various military groups, comparable data is not available from civilian populations. The latter are of particular importance, not only because of the absenteeism which the streptococcal epidemic induces, but because it would be particularly advantageous to curb streptococcal infections among school children where the hazards of complications such as rheumatic fever are particularly great.

In the one community, 95 per cent. of the school population of 500 students, school teachers, bus drivers, and administrative personnel received 250,000 units of penicillin G, twice daily for 10 consecutive days. Permission to provide such treatment was obtained from almost all parents, and the drugs were administered by the home room teachers. Each pupil was given a suitable number of pills to take home for the week-end. Children who had histories of penicillin sensitivity were given tetracycline, 250 mg. twice daily, in place of the penicillin. 24 per cent. of the students, administrative and teaching staffs, and bus drivers were cultured before the institution of therapy. Subsequent follow-up cultures were obtained on the seventh day of treatment, and on the 24th and 62nd days, and all streptococcal strains were grouped and typed. Of the initial cultures, 31 per cent. were of Group A, whereas 0 per cent. of the 7th day, 5 per cent. of the 24th day, and 10 per cent. of the 62nd day cultures were of this group. Streptococcal cases disappeared quickly, and this was reflected in a decrease in carriers. Absenteeism rapidly diminished to the expected normal rate for the season.

In the other community, essentially the same kind of procedure was followed, except that the penicillin treatment consisted of one tablet of 250,000 units penicillin G on each of 10 consecutive days. Of the culture sample obtained the day before treatment was begun, 38 per cent. contained Group A streptococci; this fell only to 20 per cent. on the 10th day (last day of treatment) and it rose to 32 per cent. on the 24th day, and 38 per cent. on the 55th day. The disease rate followed this curve, and shortly after the last culture sample was obtained the school authorities closed the school. Additionally, in this second community, the families of 56 students were cultured before the institution of treatment and several weeks after its completion. The non-school family members were not treated but were studied for the frequency of streptococci among them in relation to the school population.

Only one penicillin reaction was observed in both studies and that occurred in an adult. It is of interest that more successful regimen is similar to that which has been found most effective in military studies.

**Discussion.—**DR. CURRIER MCEWEN (New York, N.Y.): It seems to me that one of the most important aspects of this paper is its bearing on current views on the prophylaxis of rheumatic fever by prevention of streptococcal infection.

I gather from your data that positive cultures were present before the penicillin was given in the majority of instances, and that when cultures were positive later it represented the reappearance of the same streptococcal strain that the patient had carried before treatment was begun.

I wonder how many of your patients with positive cultures after penicillin had been started, were patients whose throat culture had been negative at the start and became positive later.

May I have an answer to that question before I comment further?

**DR. POSKANZER:** Only one individual acquired streptococci during the course of the study. There were a large number who retained the same type during the 10 days of therapy.

**DR. CURRIER MCEWEN (New York, N.Y.):** Then, if I may comment further it seems to me that this is of key importance in the whole programme of penicillin prophylaxis or rheumatic fever prophylaxis as advised by the American Heart Association, on the recommendation of the Committee on Prophylaxis of the American Council on Rheumatic Fever and Congenital Heart Disease. In the regimens recommended there is a very sharp difference between that for continuous prophylaxis to prevent the occurrence of haemolytic streptococcal throat infections in patients who do not already have them, and
that for the patient who is already infected. The prevention
can be achieved with relatively low blood levels, but,
it takes a higher blood level to get rid of the carrier state
in the patient who is already infected.

It is important for us to have that in mind in interpreting
your results, because they bear out very emphatically
the importance of the regimen recommended by the
American Heart Association, namely, that if one is
attempts to clear up a haemolytic streptococcal carrier
state which is already present, a single dose of 250,000
units of oral penicillin a day for 10 days is not enough.
Indeed, the recommendation of the American Heart
Association for this purpose is 250,000 units three times a
day, and the dose of 250,000 units once a day is
recommended only for continuous prophylaxis to prevent
fresh infections.

Dr. Poskanzer’s report is a very clear demonstration of
the fact that one must use more than one oral dose a day
to wipe out infection which is already present, and, also,
that it is necessary to continue that prophylaxis for the
full 10-day period rather than just for a couple of days,
as is so commonly done.

Dr. Alvin F. Coburn (Chicago, Ill.): I should like to
emphasize one point which is frequently neglected, and
that is that strains of the haemolytic streptococcus may
vary greatly in their sensitivity to anti-bacterial agents.

It has been difficult and is perhaps still impossible to
know what the future will bring forth in the sensitivity
of Group A streptococci to antibiotics. When penicillin
was first being tested it was given by us intramuscularly,
1,000,000 units a day for 4 days. One group of ten men,
all of whom had Type 6 in their throat flora, developed
negative throat cultures. A week later haemolytic
streptococcus Type 6 reappeared in the throats of six or
seven out of the ten patients, and one developed a
bronchopneumonia.

More recently we had in our staff an outbreak of
pharyngitis with Type 19. We were especially anxious
to have these persons on duty, they were given 1,000,000
units of penicillin a day in five oral doses. At the end of
5 days penicillin was discontinued. Six out of nine of
this group not only developed positive throat cultures
but also evidences of disease with slight fever and sore
throat. Each recurrence was accompanied by Type 19
in the throat flora. Five had repeated 5-day courses, but
one of them remained a carrier for months.

It seems to me possible that, whereas 250,000 units or
500,000 units may be effective as prophylaxis for certain
strains of haemolytic streptococcus, there will be others,
either present now or to come in the future, that will
require a yet larger dose of penicillin to give effective
results.

Dr. Poskanzer: As far as I am aware, there is no
published evidence indicating that there is a difference in
sensitivity to penicillin among the various types of
Group A streptococci. We have evidence that there is
a difference in sensitivity among the different groups,
and that among these groups, non-Group A streptococci
appear to be more resistant than the Group A organisms.

Dr. Milton Markowitz (Baltimore, Md.): It is
appropriate to mention a recent epidemic of streptococcal
infection that occurred in a convalescent home for
rheumatic patients, where we followed the recommenda-
tion of the American Heart Association, and used 200,000
units of oral penicillin once a day among children who
received the drug under close observation. I might also
add that our own previous experience with this dosage
was good.

During the outbreak in question we found that eleven
of the 33 patients developed clear evidence of Group A
infections. I think one-third of these quite clearly
indicates a failure of 200,000 units once a day to prevent
streptococcal infections.

The material presented here points out that there may
be a dosage factor for the prevention of streptococcal
disease, particularly in a semi-closed community where
there is repeated exposure to a virulent organism.

It would be advisable for the future recommendations
of the Heart Association to take this into account.

Dr. Currier Mcewen (New York, N.Y.): Could I
make just one further comment concerning our experi-
ence in Baltimore?

At a recent meeting of the Council on Rheumatic Fever and Congenital Heart Disease there was discussion of
some data which suggest that, even for continuous
prophylaxis, a single dose of 250,000 units daily may be
insufficient. This, however, is not yet certain.

Dr. Poskanzer: I was not aware this recommendation
was forthcoming.

Dr. G. H. Stoller (Chicago, Ill.): As a member of
the rheumatic fever prevention committee of the
Council on Rheumatic Fever and Congenital Heart
Disease, I feel I should comment at this point.

The revised recommendations of the committee are not
yet ready for official release. Inasmuch as Dr. Mcewen
has indicated that there will be a change in the recom-
manded dose schedule of oral penicillin for continuous
prophylaxis in the rheumatic subject, I think a word of
explanation is in order. The committee will suggest
that it is safer to administer 200,000 to 250,000 units of
penicillin orally twice daily, rather than once daily.

This change is not based on any evidence that the
resistance of Group A streptococci to penicillin has
changed. Rather, it is based on reports from a few
studies in progress which indicate a somewhat higher
incidence of breaks-through of streptococcal infection
than was anticipated in patients receiving single daily
doses of 200,000 units of penicillin orally. When such
breaks-through have occurred the organisms have not
been penicillin resistant. It is difficult to interpret
whether such breaks-through are based upon poor
co-operation of the patient, that is, failure to take medica-
tion regularly, or whether the dose itself is inadequate.

In some studies, like those of Dr. Markowitz
previously mentioned, some breaks-through have
occurred in patients who apparently have taken medica-
tion faithfully; the committee therefore considered a dose
given twice daily as a safer recommendation, so that there
is less chance of a full day’s prophylaxis being omitted.
The recommendation does not mean there is any known
change in the virulence or penicillin sensitivity of the
streptococcus.

I should also like to comment on the implications of
the present study with regard to the prevention of first attacks
of rheumatic fever. Under present civilian conditions, the
most common source of streptococcal epidemics is in
school children, and the control of these is one of our
problems. With more careful studies of such epidemics and adequate
public health measures designed for their early detection,
we should be in a position to stamp them out promptly
by the proper penicillin treatment of patients and
contacts in the manner presented by the authors. This
should reduce the incidence of rheumatic fever signifi-
cantly. Minor differences in the penicillin doses employed
to treat streptococcal pharyngitis successfully
are difficult to interpret, but there is general agreement that, if oral penicillin is used, at least 500,000 units or more must be given daily for at least 10 days. If penicillin is used parenterally, a single dose of 600,000 to 1,200,000 units of benzathine penicillin should be adequate.

Dr. Joseph E. Warren (Pittsburgh, Pa): I hope some of the people reporting such "breaks-through" in penicillin prophylaxis will take the opportunity later to retest the same patients to see if they effectively absorb penicillin.

Dr. David C. Poskanzer (Albany, N.Y.): One of the important points demonstrated by this study is that mass prophylaxis in school groups is a practical measure. We were impressed with the efficiency with which the school administration managed the programme. It appears that this method may have wide application in school epidemics.

Corticosterone Secretion and Metabolism in Normal Children and in Patients with Rheumatic Diseases.

By Edwin R. Hughes and Robert S. Ely, Salt Lake City, Utah. (Introduced by Dr. Vincent C. Kelley.)

The role of adrenocortical steroids in the production of collagen diseases clinically is largely speculative. However, the beneficial results of hormone therapy in such diseases, and the production of similar lesions experimentally indicate that this role is fundamental. Moreover, the evidence of a change occurring with age in the pattern of adrenocortical secretion might help further in explaining the differences observed between children and adults in the clinical manifestations of collagen diseases.

In these studies, plasma steroids were measured in children of different ages and in subjects with rheumatic disease. Plasma 17-hydroxycorticosteroids were determined by the method of Nelson and Samuels (1952) and corticosterone (Compound B) was measured by a modification of the fluorometric method of Sweat, a technique which also measures 17-hydroxycorticosterone (Compound F). In the fluorometric method, the elution fraction containing Compound B may also contain other substances with fluorescent activity, for simplicity, however, this elution fraction will be called "Compound B".

In normal age groups, the mean B values of 5.5 ± 0.58 μg per cent. for cord blood and 4.9 ± 0.65 μg per cent. for the first week of life were significantly greater than those of 3.2 ± 0.45 μg per cent. for the 6 to 17-year age group and 3.0 ± 0.21 μg per cent. for adults. The increase in Compound B levels in response to ACTH was 4 to 5 μg per cent. (over fasting levels) in children under 10 years, but only 1.5 μg per cent. in the 11 to 17-year age group.

In different collagen disease groups, the mean levels for Compound were elevated over normal: 5.6 μg per cent., compared with 3.2 μg per cent. Also, the B response to ACTH was much greater in collagen diseases: an increase of 6.6 ± 0.55 μg per cent. compared with 2.9 ± 0.61 μg per cent. Compound B values also were significantly elevated in inactive rheumatic children and their parents, but were only equivocally elevated in their siblings.

In normal subjects, 17-hydroxycorticosterone and Compound F responses to ACTH were of similar magnitude. However, in subjects with collagen disease, the 17-hydroxyecorticosteroid response was significantly greater than that for Compound F.

After the exogenous administration of Compound B, normal children had a B half-life of 39 ± 2 - 7 min.; in contrast, children with active collagen disease had a B half-life of 69 ± 6 - 7 min. Similar studies for Compound F showed a definite prolongation of the half-life in children with active collagen disease, but an essentially normal half-life with inactive disease.

Thus, it appears that Compound B values are influenced by a factor of age and that the secretion and metabolism of certain corticosteroids are altered in children with collagen diseases.

Discussion.—Dr. James B. Wyngaarden (Bethesda, Md.): I should like to speak briefly about the measurement of corticosterone in human plasma, by an isotope dilution technique developed at the National Institutes of Health by my associate, Dr. Ralph E. Peterson. In this method, the steroids are extracted from plasma with methylene chloride. This extract then contains a number of steroids and other substances, including a minute quantity of corticosterone. To this extract is added a small quantity of corticosterone labelled in carbon-4 with C14. The extract is then chromatographed on paper, and the corticosterone eluted from it. One fraction of the eluate is then analysed for C14 content, and another for corticosterone by a fluorescence technique. From these determinations the specific activity of the corticosterone may be calculated and compared with that of the labelled corticosterone originally added. From the change in specific activity of the corticosterone a dilution factor may be calculated. This is a measure, in turn, of the amount of corticosterone originally present in the extract of plasma, and from knowledge of this value the concentration of corticosterone in 100 ml. plasma may readily be obtained. This is a sensitive, accurate, and specific method.

By this method the level of corticosterone in plasma is considerably lower than that reported here to-day, and also considerably lower than those obtained with other methods by other investigators. The true corticosterone level appears to be about 1 μg per cent. in normal adults, ranging from 0.5 to 2.1 μg.

I think the non-specificity of the technique employed in the present study limits somewhat the confidence one can place in corticosterone levels of 3 μg per cent. or more, and also that in the interpretation of the changes reported. It would be interesting to repeat these studies with the more specific method for corticosterone determination developed by Dr. Peterson.

Dr. Gerald P. Rodnan (Pittsburgh, Pa): Study of children with other categories of illness, as well as of healthy children, would provide more adequate "control" data for interpretation of the findings just presented. I wonder whether the speaker has such information on other disease states apart from the collagen group.

Dr. Hughes: I appreciate the validity of the comments made by Dr. Wyngaarden. We realize that this tech-

Since the plasma concentration of free hydrocortisone probably reflects most closely the amounts available to the tissues, we have measured these plasma levels in a series of ten normal and fourteen rheumatoid subjects.

Studies by others have demonstrated in normal subjects that the lowest concentration occurs at night and that peak levels occur at 8 a.m. Thus the eosinopenia and uricosuria which reach their maxima at 11 a.m. in normals are metabolic effects of the preceding high hydrocortisone levels.

Patients with rheumatoid arthritis suffer from stiffness on arising in the morning. This symptom disappears in the next few hours. We thought this relief of stiffness might also represent an effect of the higher morning levels of hydrocortisone.

We therefore measured the plasma corticoids around the clock at 3½-hr intervals. The rheumatoid patients had mildly to moderately active disease. None had fever nor had they been on hormonal therapy. Aspirin was omitted on the preceding morning. The 7 a.m. specimen was drawn before the subjects were allowed out of bed, usually within a few minutes of awakening.

In normal subjects the low point was observed at midnight or 3.30 a.m., whereas the peak levels were at 7 or 10 a.m. This agrees with the observations of other workers.

In the rheumatoid patients a normal pattern was seen in two with minimal rheumatoid activity. In the others the concentrations at 3.30 a.m. were higher than normal and showed a smaller rise toward 7 a.m. Thus the peak concentration appears at 7 a.m. and could explain the disappearance of stiffness during the latter part of the morning. We have no satisfactory explanation for the higher levels in the rheumatoid patients at 3.30 a.m.

Discussion.—Dr. Richard D. Miller (Pasadena, Calif.): In two patients with very severe rheumatoid arthritis, we have done a complete adrenalectomy. We have observed these patients for almost 2 years since surgery. Stiffness has virtually disappeared in both of them, although there is some pain and some minor swelling.

President Robinson: Those patients obviously were maintained on corticosteroid therapy.

Dr. Miller: The two patients referred to were on steroid therapy for 4 years before surgery and both had severe rheumatoid arthritis with the characteristic morning stiffness. Steroid therapy was maintained after surgery.

Dr. Daniel Bachman (Boston, Mass.): We have also been interested in the problem of morning stiffness, and we have turned our attention to some of the normally occurring physiological rhythms in the body. One of the oldest and best known is the diurnal rhythm of urinary chloride excretion. During the day a normal individual excretes from two to three times as much chloride in the urine as during the night.

In fourteen patients with rheumatoid arthritis, we performed preliminary studies in which the chloride excretion in the urine was measured during the day...
period 8 a.m. to 8 p.m., and during the night from 8 p.m. to 8 a.m. Urine was collected for six consecutive 12-hour periods.

Of the fourteen patients, six showed a reversal of the diurnal pattern, with a greater excretion of chloride in the urine during the night than during the day. Four showed what we have called suppression of the normal day-night pattern, in that there was approximately an equal amount of chloride excreted in the urine by day and by night. The remaining four patients showed normal rhythm.

We are not yet prepared to draw any conclusions concerning these preliminary observations. Extension of these studies should include control of factors such as the total amount and time distribution of chloride intake, the amount of physical activity, posture and whether the patient sleeps at night or lies awake. However, I think our findings are of interest in relation to the data presented in the preceding two papers.

DR. JAMES B. WYNGAARDEN (Bethesda, Md): Dr. Peterson and I have been interested in the problem of adrenal hydrocortisone production and have recently published data on the size and rate of turnover of the miscible hydrocortisone pool (Wyngaarden and Peterson, 1955). This study involved the injection of a small dose of labelled hydrocortisone and the measurement of the rate of change in specific activity of circulating hydrocortisone. Specific activity falls only by virtue of the addition of newly formed, labelled hydrocortisone from the adrenal. It is not influenced by changes in the rates of degradation or excretion.

We have studied a few individuals at both 8 a.m. and near midnight, and found a decided decrease in rate of steroid production late in the day. Average adrenal production of hydrocortisone in the morning is equivalent to about 17 to 29 mg. hydrocortisone a day. In one individual, whose rate of hydrocortisone production was 1.22 mg./hr in the morning, a decline to 0.51 mg./hr was observed in the late evening.

We also used large doses of hydrocortisone and measured the rate of disappearance of hydrocortisone from the plasma. We find there is no appreciable difference in the rate of disappearance of the steroid in the morning or evening. Furthermore, the diurnal rhythm in the plasma level of hydrocortisone is reflected in a similar pattern of urinary steroid excretion except there is approximately a 2-hr lag.

Taking all this data into consideration, we believe diurnal variations result from variable rates of adrenal hydrocortisone production and have little to do with changes in excretion or metabolism rates.

DR. WALLACE GRAHAM (Toronto, Canada): Has Dr. Warren studied the morning stiffness problem in patients suffering from so-called fibrositis or psychogenic rheumatism?

DR. JOSEPH J. BUNIM (Bethesda, Md): Granted that patients with rheumatoid arthritis have stiffness in the morning, and granted that stiffness disappears several hours after a maximum level of hydrocortisone in the plasma is attained, are we warranted in regarding these two phenomena as cause and effect? The essayists imply that the 7 a.m. plasma peak dissipates, hours later, morning stiffness; but this still remains to be proved. Indeed, morning stiffness seems to coincide temporarily with the maximum plasma concentration of hydrocortisone.

DR. RICHARD D. MILLER (Pasadena, Calif): I should like to add that these patients who underwent surgery had been observed constantly for 4 years before surgery, and that morning stiffness in these patients was very marked, and has now disappeared. This is not simply a matter of steroid levels after surgery.

DR. JOHN LANSBURY (Philadelphia, Pa): In trying to correlate morning stiffness with the eb and flow of plasma hydrocortisone levels, we should not forget that patients who are subject to morning stiffness are also subject to recurrent stiffness after resting during the day. This diurnal "jelling" I look upon as "morning stiffness in miniature", and it does not appear to be correlated with plasma steroid levels; it may be that morning stiffness is likewise unrelated and is due, rather, to prolonged muscular and articular inactivity.

DR. ARTHUR A. HELBAUM (Oklahoma City, Okla.): I speak as a member of a Pharmacology Department. Much of our activity at one time was devoted to the measurement of the blood levels of various chemicals and compounds. Many of us are now wondering about the significance of this type of measurement, and the same scepticism may carry over to the determination of blood levels in clinical laboratory procedures. Our students sometimes facetiously remark that "at least our patients die in electrolyte balance".

The type of work reported in the preceding papers is important and essential; but we must remember that the blood stream is but a highway of transport and that the concentration of the substances found there may or may not be related to the functional concentration or activities of these substances found at the beginning or end of their transportation in the blood stream.

DR. WARD: In answer to Dr. Graham's question, I can only say that, in our patients with psychogenic rheumatism, the levels at 8 a.m. corresponded very closely to those seen in normal individuals and in rheumatoid patients. As yet, we do not have a large enough series of "primary fibrositis" to comment.

We should like to study steroid concentrations at tissue level, but at present, we have no way of doing so.

DR. WARREN: Dr. Miller's report on the effect of adrenalectomy is fascinating. I would agree that it is quite possible that the stiffness is produced by some other mechanism than a disturbance in hydrocortisone metabolism.

Also in answer to Dr. Bunim, we did not think we could relate the presence or total absence of stiffness with hormonal levels in the group as a whole, because "normals" are insufficient controls, but we related the tendency for stiffness, already present, to increase and decrease with the rise and fall of corticoid levels in the preceding hours.

That also partially answers Dr. Lansbury's question. We agree that other factors, including physical immobility will produce variation in stiffness.

Dr. Bachman's report that the rheumatoid patients show a continued excretion of water and chloride at night may be explained by these high night time levels of cortisone that we have observed in many patients.

Quantitation of Activity, Spread, and Deformity in Rheumatoid Arthritis.* By JOHN LANSBURY, Philadelphia, Pa.

Since the aetiology of rheumatoid arthritis is unknown.

* (Based in part on data from twenty physicians cooperating with the CENТА programme in 1955.)
its severity, its course, and its response to therapy must be judged indirectly by its inflammatory manifestations. These may be articular, or systemic, or both. In order to test an index of the severity of rheumatoid "activity", serial observations must be recorded as the disease pursues a presumably steady course between two identifiable points:

1. The state when therapy is instituted,
2. The state of full clinical remission.

The following indices of systemic rheumatoid activity declined in a regular manner as patients went into remission, and are therefore accepted as quantitative indicators of rheumatoid activity:

1. Maximum 5-minute Cutler erythrocyte sedimentation rate.
2. Degree of anaemia.
3. Duration of morning stiffness.
4. Daily aspirin consumption.
5. Hours of activity before fatigue.
6. Weakness of hand grip.

For various reasons, fever, rest pain, and abnormal serum proteins are unsuitable as indices.

The percentage values for gradations of each index are given in a Table. By averaging their sum one obtains an "Index of Rheumatoid Activity". Not more than 5 or 6 minutes is needed for gathering the basic data and making the calculation. Our results suggest that this index is sufficiently accurate both for clinical use and for the evaluation of therapeutic responses at the research level.

Joint findings may also be summed up and expressed in a single figure as a percentage of total possible involvement. Studies of the area of articulating surfaces of all peripheral joints are given in Tables. These areas are proportional to joint size, so that, by referring to them, it is possible to calculate the total "amount" of arthritis. (Further refinements, such as summing up degrees of joint inflammation and deformity, are also possible but are too time-consuming for routine use.)

Discussion.—Dr. Otto Steinbrocker (New York, N.Y.): I think Dr. Lansbury is to be congratulated for the persistence and zeal with which he has attempted to find some method of measuring the activity and therapeutic response of patients with rheumatoid arthritis.

For many years I was interested in this subject, and I know it is a difficult and complicated one. The greatest pitfall, of course, is the attempt to quantitate subjective information. If the mathematical and calculus-like method he has devised can overcome the difficulties of quantitating much of this information, I think it should be very valuable.

I hope for his sake that before this study is completed—or possibly I should reverse it and say I hope for the patients' sake that by the time this method has been worked out, a truly specific therapeutic agent will become available. All these complicated indices then would hardly be necessary, because it will be very obvious, when we have such an agent, that the patients respond.

Dr. Lansbury: I should like to add that, although the reasoning behind this method may appear complicated, the application of the method is simple and requires only a few minutes of the clinician's time for recording the data and making calculations from Tables.

Furthermore, many of the items which we ordinarily think of as being "subjective" have been proved to be objectively determinable. For instance, I have found that most patients can give a very accurate account of the duration of morning stiffness. The constancy and reliability of these observations is proved by the regular rate of decline as patients go into remission, and the same thing may be said for the other observations.

Dr. Joseph L. Hollander (Philadelphia, Pa.): This ingenious method set up by Dr. Lansbury has a great deal of merit. I think all of us have been looking in vain for some years for a rapid and easy laboratory test which will show just how severe each case of rheumatoid arthritis is so that we can gauge its progress. Certainly we all know that the erythrocyte sedimentation rate is not such a test.

Until we do find such a test, or until we have a cure for this disease, we must develop some means of standardizing clinical evaluation.

Dr. Lansbury's method, which I have had the opportunity to try out, is the best I have seen.

Dr. Lansbury: I thank the discussors and again make a plea that many of you will try out the method. I shall be happy to send any interested clinicians the necessary details and Tables on request. In the meantime we plan to gather data on about thirty to fifty remissions so as to arrive at an authoritative statistical evaluation of each item and see how it should be weighted.

Dr. John H. Vaughan (Richmond, Va.): As I understand it, your 100 per cent. figure which refers to the average of a group of patients observed during a given period. The reference standard is your clinic patients or private patients. This means that, if we were to use your 100 per cent. value, then other studies of rheumatoid activity in a given patient would be referred to Dr. Lansbury's 100 per cent. In other words, it would show the activity of a given patient with respect to your average.

Would it be possible to work this thing out, so that we all started from a zero base line, and so achieve an absolute measure rather than one related to this particular series?

Dr. Lansbury: I should be delighted if those interested would send such information. To take another example, however, the data on which we based the average value for the Westergren sedimentation rate was furnished almost entirely by Drs. Duff and Ziff.

I doubt whether securing data on, say, 1,000 cases would greatly alter our average values. Nevertheless, we shall try to collect these data by a "spot check" from a hundred clinics.


Since 1927 those concerned with gold salt therapy in rheumatoid arthritis have been debating the effect of this medicament. Many believe it will alter the course of rheumatoid arthritis and have speculated vigorously and unfruitfully on the therapeutic action of this heavy metal. Freyberg's excellent metabolic studies on gold salts in the body failed to reveal any common denominator. On identical amounts of gold one patient will do very well and the next will not. We recognize this dichotomy but still feel that gold salts are clinically useful.
Some years ago we first noted the marked clinical improvement in patients with definite gold "sensitivity" skin reactions. This paper presents 49 such patients, 35 females and fourteen males, between 20 and 78 years of age, who had 54 remissions. Rheumatoid arthritis had been present from 6 months to 30 years; 44 had 90 to 100 per cent. clinical improvement, and the remainder 50 to 90 per cent. The amounts of gold causing reactions varied from 100 to 1,600 mg. (average 600) mg. The blood sedimentation index became normal within 2 to 4 weeks in 38 of 54 remissions. 27 remissions ended after 3 to 36 months (average 15). 27 are still in remissions after periods ranging from 3 months to 5 years. Changes in sedimentation rate and 17-hydroxy-steroid excretion levels during "sensitivity", and preliminary data obtained with Dr. Joel C. Goldthwait on circulating antibodies, tuberculin- and immediate-type allergic skin reactions, gamma-globulin levels, and liver function tests during gold salt treatment and during "sensitivity" reactions were observed.

Discussion.—Dr. Richard T. Smith (Philadelphia, Pa): This particular phase of rheumatoid arthritis has been of great interest to us for some time. We tried to correlate, first of all, some data that might indicate why some patients respond and some do not.

On the basis of average doses of gold for different types of patients, we theorized that the accumulation level may make the greatest difference.

We have tried to put this together on a theoretical basis, reasoning that there is probably a 1 mg. per day excretion of gold. The curve showed rapid increase in the accumulation levels, showing a loss from one injection to another. There is a tolerance level, and if this is passed, we have evidence of toxicity or of a sensitivity reaction. There is also a minimum therapeutic level that varies considerably from patient to patient.

We see the amount of gold as actual gold, not as total dosage, and we toyed with the idea of giving gold up to the point of toxicity, since in the process a remission was bound to occur.

After watching many patients, we give a maintenance dose every 3 weeks in order to replace what is being excreted. A patient on a maintenance dose may from time to time begin to show evidence of exacerbation, and in such instances we give an immediate injection, and begin to raise the accumulation level. As the disease activity decreases they are put back on maintenance dosage. Some patients seem to be unable to tolerate a 3-weekly maintenance dose. Consequently, we have made a study of urinary excretion of gold.

After approximately 6 months of study, choosing patients with high and low tolerance levels (as low as 35 mg. gold salts), some in between, some just starting gold therapy, and some on maintenance dosage for 6 months, we begin to see a pattern that suggests that the variation lies not so much in a flexible tolerance level from patient to patient, as in the amount of gold excreted from day to day.

When we have a patient that develops a sensitivity reaction, we stop the gold, wait for the toxic effect, and then reinstitute gold at a lower level that is tolerable to him, without giving time for an exacerbation to occur.

Apparently we need to approach the patient's tolerance level very closely to obtain a good remission. We should not force every patient to the toxicity level, but I do believe that most patients should have some gold given to them, and that a safe dosage system can be found.

Dr. John W. Sigler (Detroit, Mich.): I should like to describe an experience we had in our clinic that varied slightly from these described by Dr. Bayles.

This patient had active rheumatoid arthritis and had received gold therapy at regular intervals for about 18 months. She was doing some spray painting in a closed room and shortly thereafter developed an extensive exfoliating dermatitis of the exposed areas of her skin. Her rheumatoid arthritis improved and, before her discharge from the hospital, she appeared to be in remission. This episode occurred 3 years ago and she is still in remission.

Dr. Russell L. Cecil (New York, N. Y.): All rheumatologists with extensive experience with gold know that gold dermatis can bring about remission or near remission in these patients.

I always ask the patient whether he would rather have the very pruritic gold rash, or the pains of arthritis. More than one patient has said he preferred the arthritis. Be that as it may, this study is based on a nice observation, and I am glad to see it on our programme.

I should like to ask two questions: every now and then, we see patients who develop an exacerbation of pain and joint swelling with each injection of gold, so much so that after four or five injections we have to discontinue gold treatment entirely. Now, this exacerbation from gold salts was not accompanied by any sign of toxicity except a sharp increase in pain and swelling, and the patient had the impression (and so did I) that the exacerbation was related to the injection.

Secondly, having obtained good results with gold, it is very disappointing to see the almost inevitable return of arthritis a few months or maybe a few years later. The second course of gold is not so effective, and does not bring about a remission in so many cases as it did the first time. Has Dr. Bayles observed this, and if so, has he any explanation for it in relation to sensitivity?

Dr. Robert C. Battersman (New York, N. Y.): Is it necessary to treat rheumatoid arthritis patients with gold compounds to the point of toxicity? I know that, in my clinic and others, patients may obtain remission without the development of any toxic manifestation.

We have recently encountered several patients who have developed dermatis under therapy, in whom the skin eruption was due to the sesame oil in which the gold compound was suspended. These patients were able to continue gold therapy by means of a compound suspended in olive oil. We do not wish to intimate that all dermatis associated with gold therapy is related to sesame oil, but, in our experience, this makes up a good percentage of such patients.

Dr. Nathan R. Abrams (Cincinnati, Ohio): I have used gold sodium thiosulphate recently and have seen the same phenomenon, so it does not necessarily result from the oil used in some preparations. The remission does not occur with all types of reaction. For instance, I have seen no remission in one case who developed haematuria, one with optic atrophy (fortunately unilateral) and a few cases with leucopenia. On the other hand, a remission did occur in a patient who developed purpura.

So far as the dermatis is concerned, eosinophilia often develops before the dermatis, and the remission occurs along with the eosinophilia, which may possibly be regarded as a warning signal.
In some of the patients who had rather severe reactions, the use of BAL has liberated gold, followed soon afterwards by exacerbation of the arthritis. I prefer to use as few drugs as possible for the reaction, but cortisone and ACTH have not seemed to interfere with the remission and I have occasionally used them for the dermatitis.

DR. RICHARD H. FREYBERG (New York, N.Y.): It is stimulating to note that interest in gold therapy continues. Dr. Bayles used the word "sensitivity" in quotes, which I think is quite appropriate. Most of the evidence to date supports the likelihood that dermatitis and other undesirable features—call them "toxicity" if you wish—are due to a hypersensitivity or to an antigen-antibody reaction rather than to cellular toxicity. However, this has not been proved. All of our efforts to identify the antigen causing dermatitis have failed. We tested the various inorganic gold salts that were used as therapeutic agents, and the gold-protein complex, which we found was the manner in which gold is transported in the blood; we were unsuccessful, but the evidence strongly suggests that this is indeed a sensitivity reaction.

Some Europeans favour much higher doses of gold than we have recently felt advisable. This is because they have been, as Dr. Bayles's guide has seen, that the benefit to the patient seems to be greater when certain of these undesirable reactions occur. Some people have even felt that the reactions are necessary to produce the benefit, but we do not think so.

Some of these "sensitivity phenomena" may develop in some patients, but remain subclinical, and certain benefits occur in many patients without manifestations of toxicity.

Dr. Smith has mentioned the possibility of controlling the administration of gold salts by measuring the excretion of gold. I doubt whether this could be done. By chemical measurement of the concentration of gold circulating in the plasma or excreted in the urine, we were unable to find a "therapeutic level" above which administration is needed, or a "toxic level" below which troubles were avoided. Reasons for this may be the unpredictability of absorption and variability in the metabolism of gold from day to day; also the manifestations of toxicity are probably not exactly related to the amount of effective gold in the body. With improved methods for the quantitative determination of gold in the body fluids control of therapy may be more accurately attained.

The crux is that gold salt therapy is potentially valuable in the treatment of rheumatoid arthritis, but that we still do not know the mechanism whereby benefits are produced, or toxicity results.

DR. ROTHSCHILD (Kansas City): How do you manage dermatitis and what trouble do you have with depression of bone marrow in patients?

DR. BAYLES: I am delighted that so many people feel so strongly on this subject.

First, regarding Dr. Smith's remarks about the possibility of finding a level of serum gold which could be maintained with a favourable effect on rheumatoid arthritis, I am inclined to agree with Dr. Freyberg that there is no close correlation between the amounts of gold given and the toxic effect.

Dr. Sigler mentioned a case of exfoliative dermatitis thought to be due to paint who got complete remission of rheumatoid arthritis at the time of the dermatitis. Incidental dermatitis in patients receiving gold, such as dermatitis medicamentosa, nummular eczema, extensive seborrhoeic dermatitis, sunburn, and other irritations of the skin, do not cause remissions of rheumatoid arthritis, but I do not question his observation.

In answer to Dr. Cecil, some patients do complain of an exacerbation of the arthritic symptoms after the gold injection, but we do not let this alter our course of treatment. I agree that sometimes the second course of gold is less effective but in our series we have had 54 remissions in 49 patients, so that remission occurred more than once with gold salt "sensitivity" in 5 cases.

I agree with Dr. Batterman that skin toxicity is not desirable and that many patients seem to get well without dermatitis.

Sesame oil can be a sensitizing agent. However, we have not been able to reach any logical conclusion from the cross skin sensitivity study comparing sesame oil alone and gold salts alone. I agree with Dr. Abrams that gold thiosulphate salt will bring about the same sort of response as we have described. Fortunately, we have never seen optic atrophy, but we do see nephritis or mild renal irritation due to gold, which is not associated, in my experience, with clinical remission of rheumatoid arthritis. When this occurs gold treatment should be stopped.

Dr. Freyberg has stimulated me in going ahead with this problem through the last 2 or 3 years. I agree with him that this reaction is probably due to "sensitivity" rather than to toxicity. I have not used higher doses than those mentioned because the only two deaths that we have had at the Robert B. Brigham Hospital or in my practice were of patients receiving more than 50 mg. a week. I think, if this therapeutic mechanism is going to operate, it will operate at a relatively safe level. Of the several hundred patients who have received gold, only two died, and they were receiving more than 50 mg. a week. This may be only a coincidenc.

As to the question of handling the dermatitis, we have treated it in the classical fashion with B.A.L. (British Anti-Lewisite) and cortisone, usually in combination.


22 patients were the subjects of this current study to determine the adrenocortical responsiveness to the stimulus of corticotropin after continuous therapy for 4 to 6 years with cortisone (daily doses ranging from 37.5 to 87.5 mg., or equivalent). This response was measured by significant increases in 24-hr excretion of urinary 17-ketosteroids and free corticoids, and by decrease in the number of circulating eosinophils.

According to predetermined and arbitrary criteria, all patients showed a definite response within 5 days. There was no correlation between the daily dose of cortisone or the duration of treatment and the adrenocortical response to corticotropin.

Fourteen of these patients had been subjects of such studies in previous years, and were now being studied for the last 2 years. These successive tests, identical for each patient and unvaried from study to study, permitted a serial demonstration of adrenocortical response in each, and a comparison between patients receiving long-term treatment with cortisone. In these fourteen patients, no...
consistent trend in adrenocortical responsiveness to corticotropin could be demonstrated.

Discussion.—Dr. Joseph J. Bunin (Bethesda, Md): This study provides a sound basis for the practice of not interrupting the course of steroid therapy, or of administering from time to time ACTH to patients taking cortisone. It would be helpful if the authors could clear up one more point for us. Is there a need for the administration of ACTH upon discontinuance of cortisone? One might reason that administering ACTH might suppress the endogenous secretion of corticotropin by the pituitary and may not, after all, be as helpful to the patient as it seems.

Did the authors compare recovery time (as measured by ACTH response) in patients receiving ACTH for several successive days after stopping cortisone with the recovery rate in patients who did not receive ACTH?

Dr. Larzelere: We have not made such a comparison, but it would be helpful to do so.

Effects of Hydrocortisone, Prednisone, and Prednisolone on Gastric Secretion in Humans. By W. H. Kammerer and A. L. Rivelis, New York, N.Y.

Studies were made of the effects of hydrocortisone, prednisone, and prednisolone on gastric secretion in individuals with rheumatoid arthritis (some of whom had had a peptic ulcer during steroid therapy), and in twelve volunteer non-arthritic subjects. Total secretion and viscosity determinations for a 24-hr period were made and hourly determinations of free HCl and pepsin excretion for a 24-hr period were measured. The corticosteroids were then administered orally in varying doses and sequence for 5 or more days, after which similar aspirations and analyses were made; in some subjects the effect of concomitant antacid and anticholinergic agent administration was also studied.

In six subjects (all females) receiving hydrocortisone and prednisone alternately, there was an average rise of 10 units of free HCl secretion over basic levels. Total 2-hr secretion was increased and viscosity slightly lowered after administration of the steroids. No significant change in pepsin excretion occurred.

Similar changes were not observed in six volunteers (4 males and 2 females) receiving prednisolone, but this may have been due to a variable in the sample. Neither the dosage of corticosteroid used (varying from 7.5 to 15 mg. prednisone and prednisolone and 20 to 60 mg. hydrocortisone daily), nor the sequence in which the steroids were administered appeared to have any consistent effect upon the results. Concomitant administration of antacids and anticholinergic agents resulted in a significant decrease in the level of free HCl.

The results of these studies do not indicate changes in the secretion of free HCl or pepsin that appear to be of any significance in the genesis of peptic ulcer in subjects receiving corticosteroids.

Discussion.—Dr. James H. Barr, Jr. (Pittsburgh, Pa): Some time ago, not long after prednisone was introduced, we became impressed with the relatively high incidence of dyspepsia. This latter term was used to include symptoms ranging from mild gaseous distension to frank ulcer pain.

We, therefore, undertook a study in which x-ray examination of the upper gastro-intestinal tract and gastric analyses (Ewald meal) were performed on six rheumatoid arthritics before and after prednisone therapy, and on ten rheumatoid patients after the institution of prednisone therapy. On the group of six in which the studies were done before and after therapy, the Ewald gastric analyses included pH, and free and total acid measurements. In five of the six cases studied, there was an increase in free and total acidity with a drop in pH values. This increase was statistically significant, but was not as high as those usually observed in patients with peptic ulcer. None of these five patients developed peptic ulcer, the sixth patient did so.

In the group of ten patients studied after the start of prednisone therapy, x-ray examination revealed two duodenal ulcers (niches) and one hiatal hernia with bleeding. On 30 to 40 mg. prednisone daily and a strict physiological antacid regimen, one ulcer healed, and one decreased in size by 75 per cent., while the bleeding from the hiatal hernia stopped.

One of our patients was a 58-year-old white male with long-standing rheumatoid arthritis. He was the only one of the six patients studied before and after therapy who developed a frank duodenal ulcer. His response to an Ewald test meal and a histamine injection was entirely normal before the onset of therapy. Hydrocortisone, 45 mg. daily, did not increase gastric acidity significantly although a duodenal ulcer niche was found by x-ray. Prednisone, 40 mg. daily, did increase acidity, but the ulcer crater decreased in size by at least 75 per cent. and gastric symptoms disappeared. He was on a rigid ulcer regimen during this period of prednisone therapy. The dosage of prednisone has since been reduced to 10 mg. daily, and the duodenal ulcer is now completely healed as indicated by x-ray examination and clinical findings.

I would like to emphasize that, though prednisone may increase gastric acidity as shown by the response to an Ewald meal, we have seen no consistent correlation between this increased acidity and the presence of peptic ulcer. We have, indeed, found, as has Dr. Kammerer, that when prednisone therapy is essential for patients with rheumatoid disease who have peptic ulcer, a strict physiological antacid regimen will often permit the lesion to heal.

Dr. David H. Neustadt (Louisville, Ky): I have had the opportunity of observing a total of 47 patients with rheumatoid arthritis who have received either prednisone or prednisolone for one year or more. So far, we have been fortunate in not having any gastro-intestinal catastrophes, though some form of gastro-intestinal symptoms did occur in fifteen patients (29-7 per cent.). Upper gastro-intestinal x-ray studies were not done routinely, but radiological studies of the gastro-intestinal tract were carried out in all patients who developed any gastro-intestinal symptoms. No duodenal ulcers were found, but gastric ulcers were found in two patients (4-2 per cent.). In one of the latter, a female, the drug was withdrawn and the ulcer healed with appropriate therapy. The other patient, a male, developed a large ulcer on the greater curvature after 4 months of steroid treatment. An ulcer regimen was instituted and the prednisone was continued without altering the dosage.
The ulcer symptoms abated and its healing was followed by serial x-rays until after a month it was completely healed.

I should like to comment briefly on the recommendation of some workers that every patient given the new steroids should routinely receive concomitant antacid therapy prophylactically. I doubt that this would be sufficient to prevent the occurrence of ulcer disease, and think that this procedure may do harm by masking or suppressing the usual ulcer symptoms, so that the clinician and patient are not sufficiently aroused to request x-ray study. Then, instead of pain giving the initial signal, the patient may be introduced to his new malady by a more serious manifestation, such as sudden gastric haemorrhage or perforation. If my patient is developing an ulcer, I want to know about it as soon as possible.

Of incidental interest to this subject are some recent studies done in the Gastro-enterology Department of the University of Louisville. Cortisone was administered intramuscularly 50 mg. daily to two Dragstedt-pouch dogs for 2-3 months, after a control period of the same interval. There was no increase in output or volume of HCl. This is in contrast to work by others with ACTH in dogs, in which HCl output was stimulated in the presence and absence of both the vagal and antral mechanisms. Although these results are of limited clinical interest owing to differences in pharmacological response, they demonstrate the absence of influence by a profoundly potent steroid in the same species, when the action of both is considered so similar in humans, and may suggest some other mechanism of action as related to production of HCl in the gastro-intestinal tract.

Having previously participated in studies of gastric secretion in humans, I know the difficulties involved. I am sure the authors will not consider it amiss if I recall some of the factors that must be taken into consideration in attempting to interpret the results of gastric analyses.

1. Spontaneous fluctuation of basal gastric secretion, even in experimental conditions, in the same patient on different days.
3. Psychic stimulations to gastric secretion produced by sight, smell, food, or suggestion during tests.
4. Possible loss of gastric juice through pylorus or regurgitation of bile into stomach.

I should like to know whether any special techniques for overcoming or avoiding any of these pitfalls have been evolved.

Lastly, of course, definitive analysis is greatly handicapped by our lack of knowledge of all the factors contributing to the formation of peptic ulcer.

**Psychosomatic Study of Children with Rheumatoid Arthritis.** By GASTON E. BLOM and ROBERT T. LONG, Boston, Mass.

In this paper we report on a continuing study of emotional factors in juvenile rheumatoid arthritis. Our study is based on clinical data obtained in psychiatric interviews with 58 patients (39 girls and 19 boys), ranging in age from 1½ to 16 years of age. Common features were noted in emotional factors related to onset and recurrence, past historical events appearing to have a determining influence on the personality characteristics of mother and child, and in personality aspects of mother and child.

For further clarification of significant emotional factors, data from rheumatoid arthritis cases have been compared with similar data from other disease groups (asthma). Certain emotional factors showed a primary relation to rheumatoid arthritis in children, and were differentiated from secondary emotional factors derived from illness and hospitalization.

**Discussion.**—Dr. ARTHUR I. SNYDER (New York, N.Y.): I should like to ask for more information about the selection of the patients for your study. As I recall Dr. Ludwig’s study, the results of which you compare with yours, his patients were referred because of psychological symptoms and had rheumatoid arthritis in addition.

Dr. BLOM: Our series of cases comprised every patient that was admitted to the hospital for rheumatoid arthritis, and also every case seen in the out-patient department. At the beginning of the study we did see cases referred to us because of psychological problems, but since that time the greater number of our cases was picked up routinely by the research team.

Dr. SIDNEY COBB (Pittsburgh, Pa.): I should like to congratulate Dr. Blom on what I think is magnificent methodology in approaching a problem which we all observed, but which we have not been able to isolate in our usual clinical studies, nor in our epidemiological studies to date.

Dr. ROBERT BLACK, Boston: I have listened with great interest to this excellent paper. I am very much struck with the relationship between emotional upheavals and variations in the severity of disease and onset of disease in adults.

One of the things, however, which always puzzles me when we have psychosomatic discussions, is that the type of personality or emotional dynamics always sounds the same to me. We have aggression, throttled hostility, desires to kill the mother, all present in a variety of otherwise unrelated diseases, such as ulcerative colitis, peptic ulcer, or hypertension.

I should like to ask whether the speaker thinks there is a specific psychodynamic pattern related to arthritis or whether we are simply seeing an excessive amount of “negative energy” or “negative feeling,” which can occur in any psychodynamic situation.

Dr. BLOM: We do not believe in the personality type concept regarding the relationship of emotions to psychosomatic disease. Rather, we think there are psychological conflicts that are characteristic.

This group of patients, has some emotional similarity to ulcerative colitis patients and others with psychosomatic conditions. Our interest, however, is that there are significant differences, too, and we want clearly to differentiate these psychosomatic diseases if we can. We are impressed with the different ways these patients deal with similar situations of emotional conflict.

**Synovial Lesions in Progressive Systemic Sclerosis** (Diffuse Scleroderma). By GERALD P. RODNAN, ROGER L. BLACK, and JOSEPH J. BUNIN, Pittsburgh, Pa., and Bethesda, Md.

Arthritic symptoms are recognized to be of frequent occurrence in patients with progressive systemic sclerosis, often preceding the cutaneous and visceral manifestations of the disease. In an effort to learn more concerning
the nature of this joint involvement, synovial biopsies have been obtained from a suprapatellar bursa of thirteen consecutive patients with histologically confirmed diffuse scleroderma.

Evidence of visceral involvement was present in all but two of the patients at the time of the synovial biopsy. The synovium was found to be normal in the three patients without arthritis complaints. Ten patients in whom joint pain, swelling, and stiffness played a prominent role in the disease picture were found to have objective evidence of polyarthritis and markedly abnormal biopsies. The synovial lesions included focal aggregations of lymphocytes and plasma cells, villous hyper trophy, loss of synoviocytic lining, focal fibrosis, and sclerotic and perivascular inflammatory changes involving the smaller blood vessels. In four patients of this group. There was dense fibrosis of the synovium and the cellular infiltrations were less marked.

X-ray examination of affected joints disclosed narrowing of joint spaces and varying degrees of osteoporosis, but no destruction of bone. Sheep cell agglutination reaction was negative in nine patients and only slightly elevated in two. The clinical evidence suggests that this form of arthritic disease is distinct from rheumatoid arthritis and can be considered an integral feature of progressive systemic sclerosis.


Over half of the persons we have seen in our population study, with marked radiographical evidence of osteo-arthritis failed to report any pain at the relevant sites. Similar findings have long disturbed the thoughtful clinician as he makes a diagnosis of degenerative joint disease. This has led us to investigate the concomitants of pain in osteo-arthritis.

In the course of our examination of 478 individuals selected at random from the Arsenal Health District of Pittsburgh, we found that morning stiffness is more closely associated with joint pain than are degenerative changes visible by x-ray. This is most striking for the hands and wrists but is also true for the knees. When we limit our study to people with marked degenerative changes, we find that the greater is the amount of pain or swelling, the greater is the probability of having morning stiffness. Furthermore, we find that of these persons with marked degenerative changes, about 30 per cent. have pain and only 5-10 per cent. have pain without morning stiffness.

This strong association between morning stiffness and the presence of symptoms in those with x-ray evidence of osteo-arthritis arouses our curiosity, for it is well known that there is a marked association between morning stiffness and rheumatoid arthritis. This is a subject worthy of further investigation.

Pathogenesis of Osteo-arthritis of the Hip. By GOLDEN SELIN and HENRY JAFFE, New York, N.Y.

The natural progression of degenerative joint disease at the hip was followed in its various stages and phases from the earliest lesion of fibrillation to the advanced changes. The nature and genesis of the pathological involvement, and its peculiarities and complications were illustrated by sections of femora and the corresponding acetabular structure and pelvic bones removed during surgery or at autopsy. The thesis that osteo-arthritis is a disease of the acetabulum as well as of the femoral head, and the value for measures based on such a total concept were illustrated by the pathological alterations. The relationship of these observations to degenerative articular disease was discussed.

Discussion.—DR. CURRIER MCEWEN (New York, N.Y.): I cannot let the chance pass of saying what a splendid presentation this was. It clearly summed up years of experience and observation. I should like to offer my personal thanks to Dr. Selin.


A total of 212 arthritics was referred to a vocational rehabilitation programme in 30 months, 159 cases, including 62 (39 per cent.) who had been returned to gainful employment, being closed by March, 1956. The vocational rehabilitation programme includes:

1. Screening and evaluation, to select suitable clients;
2. Vocational counselling, to identify the patient's skills, aptitudes, limitations, and motivations, design his rehabilitation, and supply guidance throughout the course.
3. Vocational training;
4. Help in finding a suitable job.

Men and women were referred in almost equal numbers. A slightly higher proportion of men returned to work. Half the patients were aged from 40 to 59; 46 per cent. in this age group and one-fourth of those aged 60 or more found employment. The major diagnostic categories were:

- Rheumatoid arthritis
- Osteo-arthritis
- Spondylitis

Rheumatoids returned to work at the same rate as the whole group. Disability varied widely but even severe impairment did not necessarily preclude vocational rehabilitation.

The patients' ability to return to work in relation to the duration of illness was as follows:

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<th>Duration of Disease (years)</th>
<th>Percentage returning to Work</th>
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At referral, 105 patients were unemployed; 39 had never worked; and fifteen faced problems on their jobs caused by arthritis. The 62 who returned to work included 44 unemployed patients, eight without employment history, and ten who were working at referral.

Vocational rehabilitation required from a few weeks to over a year, depending on the patient's disability, skills, experience, and motivation.
Discussion.—Dr. Otto Steinbocker (New York, N.Y.): I know the hour is late but I must say a few words about this projection my own behalf and on that of my colleagues who use it in New York. This is a remarkable recent development in the management of disabled patients. It represents a step forward for a group of individuals who need to progress beyond the small amount of help we could give them.

The possibilities which Mr. Acker and his project have opened up for them are beyond anything that we could have imagined before this work was instituted.

Dr. H. S. Robinson (Vancouver, Canada): We have had a project going for some years in Vancouver, trying to return patients to work. These are patients who initially, are put in the rehabilitation centre. While they are there, they have vocational guidance, and so forth, and we have found it a successful and useful endeavour.

Could you tell me whether you have a work tolerance programme in the rehabilitation centre carried on by your occupational therapy department?

Mr. Acker: Yes. The patients in the “Back to Work” project are ordinarily people whose work tolerance had reached the maximum of about eight hours a day before they were accepted for the project. Patients are accepted whose work tolerance is less than 8 hours if it is anticipated that they may reach full tolerance when the vocational rehabilitation programme is completed (usually 9 to 12 months). There is a work tolerance project at the Institute for the Crippled and Disabled which selects patients for referral to a training programme such as this one.

Dr. William H. Kammerer (New York, N.Y.): Can Mr. Acker give us any idea of the cost per patient for this rehabilitation?

Mr. Acker: That is an extremely difficult estimation to make. The Institute for the Crippled and Disabled is a multi-purpose centre which is used extensively for teaching and research, as well as for direct services to patients. Columbia and New York Universities use it for training occupational and physio-therapists and other training programmes also operate there. I doubt whether the cost of this particular unit has been determined. I suspect that for training, the cost is relatively high, but it would not be so high if the Institute had not so many other functions. I am not in a position to give you a detailed cost breakdown.

Dr. William H. Kammerer (New York, N.Y.): “Relatively high” means different things to different people. “Relatively high” to me is $10. I wonder if you have any idea what “relatively high” is.

Mr. Acker: It really is extremely difficult to give you a dollar-and-cent figure. The Institute operates on an annual budget of about half-a-million dollars for something around 1,470 patients—I haven’t the exact figures. We can break it down from there, but it does not mean very much in terms of cost per individual patient for direct services to the patient.

It would not be satisfactory to set up a programme based on individual costs.

Course of Systemic Lupus Erythematosus during Long-Term Maintenance Therapy. By Morris Ziff, Paul Esserman, and Currier McEwen, New York, N.Y.

The course of systemic lupus erythematosus as currently observed and treated has changed since 1949. Two new influences have modified the observed life history of the disease: the introduction of hormonal therapy, and the discovery of the L.E. cell test as a criterion for diagnosis. The L.E. cell test has led to the diagnosis in patients with milder forms of the disease than were heretofore recognized; treatment with hormones has lengthened life. It is important, therefore, to review our knowledge of the life history of lupus erythematosus in the light of these new influences.

This investigation follows the course of 24 patients for up to 4 years. All but one were treated with steroids, and thirteen received combined treatment with steroids and chloroquine or Atebrin. The course of the majority of the patients receiving combined therapy has been relatively benign. All but one are alive and controlled on moderate maintenance dosage. The average duration of therapy was 18 months.

Renal function, as measured by dye excretion and endogenous creatine clearance tests, appeared to diminish slowly, if at all, in most patients during the period of observation. The degree of albuminuria tended to fluctuate significantly, and protein often disappeared from the urine for months.

Psychosis, which was present in eight patients, improved with administration of steroids. Relapse of activity, when it occurred, appeared to follow a characteristic pattern for each patient. Close supervision of maintenance therapy appeared to diminish the frequency and severity of relapses.

Sensitized sheep cell agglutination tests on the egg- albumin fraction, carried out in sixteen patients, were positive in five. In these, the character of the joint involvement resembled that seen in rheumatoid arthritis.

The course of the erythrocyte sedimentation rate, C-reactive protein test, albumin/globulin ratio, sensitized sheep cell agglutination titre, serological test for syphilis, and L.E. cell test during therapy was charted.


The incidence of mucocutaneous lesions in patients with Reiter's syndrome treated during an 8-year period at the Hines Veterans' Administration Hospital was found to be greater than that reported in other series. Thirty of the 38 patients presented perineal erosions and/or balanitis circinata lesions (80 per cent.). 23 patients had both lesions; four of the remaining seven had perineal erosions; three had balanitis circinata alone.

In addition, fourteen of these thirty patients (37 per cent. of the 38), had painless oral, pharyngeal, or glossal mucous membrane lesions. A number of others had diffuse injection of the palate and pharynx and darker red mucosal areas which possibly represented the terminal stage of previous lesions. These were not included.

Keratoderma blennorrhagica-like lesions, the keratosis of Reiter's syndrome occurred in eleven of the thirty patients with mucosal lesions (30 per cent. of the 38), nine
presented hard nodular hyperkeratotic lesions, and two had soft parakeratotic patches.

We believe that mucocutaneous lesions may be as important in establishing the diagnosis of Reiter's syndrome as are the non-specific urethritis or conjunctivitis. In equivocal cases, when urethritis and/or conjunctivitis have not been observed or well documented, the mucocutaneous lesions, known to appear 4 to 6 weeks after the onset, may be diagnostic. In the endemic form, the triad of Reiter's syndrome might better be considered a tetrad, consisting in its complete form of urethritis, conjunctivitis, arthritis, and mucocutaneous lesions.

* * *

REPORT OF COMMITTEE ON DIAGNOSTIC CRITERIA

GRANVILLE A. BENNETT SIDNEY COBB
RALPH JACOX RALPH JESSAR
MARIAN W. ROSES (Chairman)


In a disease of which the aetiology is not known and in which there is no proof of diagnosis, diagnostic criteria will assist in securing uniformity in the cases included in any discussion, study, or report of the disease, whether it be concerned with prevalence, incidence, manifestations, course, or treatment.

The classification of rheumatoid arthritis in three groups seemed the most useful way to begin.

(1) The definite group, in which there is almost no question that every patient has rheumatoid arthritis;

(2) The probable group, in which it is highly probable that every patient has rheumatoid arthritis;

(3) The possible group, which will contain chiefly patients with rheumatoid arthritis but may also include some with other diseases.

It is apparent that the first two groups will be used in any study of the characteristics, course or treatment of rheumatoid arthritis.

Since no absolute criteria applicable to all cases could be set up, the most satisfactory approach was to determine the characteristics—such as morning stiffness, soft tissue swelling, typical x-ray changes, and symmetry of involvement—which, if present in adequate number, would establish the diagnosis. Because of the similarity to the clinical findings in various other diseases it was necessary to list evidence of these diseases, which, if present, would exclude the patient from the groups diagnosed as rheumatoid arthritis. In some cases it is possible that patients with one of these other diseases, for instance one of the generalized connective tissue diseases other than rheumatoid arthritis or other rheumatic disease such as gout, may be thought to have rheumatoid arthritis also (as a patient with a history suggesting rheumatic fever and with physical findings of mitral and aortic valvular disease but also with a recent history and findings of definite rheumatoid arthritis). However, in such a situation, it seems wisest not to include the patient in a study of rheumatoid arthritis but to classify him separately and compare as desired. On the other hand, patients with rheumatoid spondylitis (x-ray changes in sacro-iliac joints or persistent limitation of motion of any region of the spine), or with psoriasis, ulcerative colitis, or onset under the age of 12, are to be included in the rheumatoid groups, if they satisfy the criteria, but should be listed separately and the findings given separately.

Rheumatoid arthritis is a systemic disease occurring at all ages, more frequently in women than men. Many of the signs and symptoms are entirely non-specific and of no value in differential diagnosis, and are therefore not included in the criteria. The majority of these are the indicators of the systemic involvement in the disease—fatigue, anorexia, weight loss, fever, vasomotor symptoms, paresthesias, lymphadenopathy, anaemia, leukocytosis or leukopenia, and increased concentration of total globulins or of α and γ globulins and fibrinogen and decreased concentration of albumin in the blood. Similarly, many of the findings are evidence of skeletal tissue inflammation and its sequelae—muscle atrophy, skin atrophy, pigmentation, tenosynovitis, and palmar fascia thickening; these are also non-specific and are not included. Pericarditis, myocarditis, and pleurisy have been omitted from the criteria because they are more frequent in other diseases than in rheumatoid arthritis and would tend to lead to the wrong inclusion of many patients. In general, patients with rheumatoid arthritis can be diagnosed by the criteria as they stand at the time they develop any of the above manifestations.

The criteria for the diagnosis of definite and probable rheumatoid arthritis have been made relatively rigid, since cases included in these groups will be used for study of the disease and often as a basis for statistical conclusions as to prevalence, incidence, characteristics, course, and treatment. However, it was considered important not to make the criteria so strict that only far-advanced so-called "typical" cases, or cases of long duration could be included. The required duration of joint symptoms (6 weeks in
definite rheumatoid arthritis and 4 weeks in probable rheumatoid arthritis) was made as short as possible without risk of making the diagnosis insecure. The duration tends to exclude the majority of cases of infectious and traumatic arthritis. Similarly, involvement of a minimal number of joints was required, two joints being sufficient if enough of the other criteria are present. The objective evidence of joint involvement, such as swelling, must be observed by a physician, but all observations need not necessarily be made by the same physician. When two joints are not involved simultaneously, they may satisfy the criterion of joint involvement if there is no interval free of joint symptoms of more than 3 months. If a longer interval has occurred, the possibility of the existence of two separate types of joint disease becomes greater. X-ray changes due to degenerative joint disease will not satisfy the criterion, but the presence of such x-ray changes will not exclude patients from the groups of rheumatoid arthritis. This proviso will lessen the likelihood that patients with mild rheumatoid arthritis who also have degenerative joint disease will be excluded from the rheumatoid groups. The nature of the mucin precipitate from synovial fluid was thought to be the most easily determined and most characteristic finding in rheumatoid fluids. Other abnormalities, especially increased activity of amino-tripeptidase or betaglucuronidase, will add weight to the diagnosis but are not included as required criteria.

The criteria for the diagnosis of possible rheumatoid arthritis are much less rigid. In this way it will be possible to pick up very early, mild, or atypical cases which might otherwise not be noted and which can be followed profitably to learn more of the course and nature of the disease. It is realized that, of necessity with such liberal criteria, some patients who do not have rheumatoid arthritis will be included in this group. However, the errors in diagnosis will, in most cases, become apparent as the group is followed, and the patients included in the “possible” group cannot be used for conclusions as to the characteristics or results of treatment of the disease.

The committee suggests that, if these criteria are acceptable, they be published now with the stipulation that they be reviewed and revised in 1959 or earlier if advisable.

PROPOSED CRITERIA FOR RHEUMATOID ARTHRITIS
MAY, 1956

Rheumatoid arthritis is a systemic disease of unknown etiology occurring at all ages, more frequently in women than men. It has been classified in these criteria in three groups—definite, probable, possible. The definitions of these states as outlined below are to be used for the identification and classification of cases for clinical study and treatment and for reporting the prevalence and incidence of the disease. The value of the criteria lies in establishing the findings necessary to allow inclusion of a patient in one or another of the groups. In this way only is it possible to obtain relative uniformity in the cases included (for discussion, study, or reporting) in any group of patients with rheumatoid arthritis (definite, probable, or possible) and to allow the comparison of a group from one source (physician or clinic) with those from other sources.

When these definitions are used, patients with rheumatoid spondylitis (x-ray changes in sacro-iliac joints or persistent limitation of motion of any region of the spine), or with psoriasis, or with ulcerative colitis, or with onset under the age of 12 should be included if they satisfy the criteria, but they should be listed separately and the findings given separately.

Any one of the exclusions listed in Section II will rule out the diagnosis of rheumatoid arthritis (definite, probable, or possible).

SECTION I

(A) Definite Rheumatoid Arthritis.—This diagnosis requires five of the following criteria and the total duration of joint symptoms must be at least 6 weeks.

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint (observed by a physician).
3. Swelling (soft tissue thickening or fluid—not just bony overgrowth) in at least one joint (observed by a physician).
4. Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms may not exceed 3 months).
5. Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of mid-phalangeal metacarpophalangeal, or metatarsophalangeal joints is acceptable without absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules (observed by a physician) (over bony prominences, on extensor surfaces, or in juxta-articular regions).
7. X-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes)—degenerative changes do not exclude patients from the group of rheumatoid arthritis.
8. Positive sheep cell agglutination (Rose and Ragan, or Heller test) or positive streptococcal agglutination test.
9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).
10. Characteristic histological changes in synovial membrane with three or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading.
marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form “lymphoid nodules”;
deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.
11. Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly peri-vascular.

(B) Probable Rheumatoid Arthritis.—This diagnosis requires three or four of the above criteria and the total duration of joint symptoms must be at least 4 weeks.

(C) Possible Rheumatoid Arthritis.—This diagnosis requires two of the following criteria:
1. Morning stiffness.
2. Tenderness or pain on motion (observed by a physician) with history of recurrence or persistence for 3 weeks.
3. History or observation of joint swelling.
4. Subcutaneous nodules (observed by a physician).
5. Elevated sedimentation rate or C-reactive protein.
6. Iritis.

SECTION II. EXCLUSIONS
1. The typical rash of disseminated lupus erythematosus (with butterfly distribution, follicle plugging, and areas of atrophy).
2. High concentration of lupus erythematosus cells (four or more in two smears prepared from heparinized blood incubated for not more than 2 hrs).
3. Histological evidence of periarteritis nodosa with segmental necrosis of arteries associated with nodular leukocytic infiltration extending peri-vascularly and tending to include many eosinophils.
4. Persistent muscle swelling of dermatomyositis.
5. Definite scleroderma (not limited to the fingers).
6. A clinical picture characteristic of rheumatic fever with migratory joint involvement and evidence of endocarditis, especially if accompanied by subcutaneous nodules or erythema marginatum or chorea. (An elevated antistreptolysin titre will not rule out the diagnosis of rheumatoid arthritis.)
7. A clinical picture characteristic of gouty arthritis with acute attacks of swelling, redness, and pain in one or more joints, especially if relieved by colchicine.
8. Tophi.
9. A clinical picture characteristic of infectious arthritis of bacterial or virus origin with:
   an acute focus of infection or in close association with a disease of known infectious origin;
   chills;
   fever;
   acute joint involvement, usually migratory initially (especially if there are organisms in the joint fluid or response to antibiotic therapy).
10. Tubercle bacilli in joints or histological evidence of joint tuberculosis.
11. A clinical picture characteristic of Reiter’s syndrome with urethritis and conjunctivitis associated with acute joint involvement, usually migratory initially.
12. A clinical picture characteristic of the shoulder-hand syndrome with involvement of one shoulder and the hand on the same side with diffuse swelling of the hand followed by atrophy and contractures.
13. A clinical picture characteristic of hypertrophic pulmonary osteo-arthritis with clubbing of the fingers and/or hypertrophic periostitis along the shafts of the long bones, especially if an intra-pulmonary lesion is present.
14. A clinical picture characteristic of neuro-arthritis with condensation and destruction of the bones of involved joints and with associated neurological findings.
15. Homogenetic acid in the urine detectable grossly with alkalinization.
16. Histological evidence of sarcoid or positive Kveim test.
17. Multiple myeloma as evidenced by marked increase in plasma cells in the bone marrow, or Bence-Jones protein in the urine.
18. Characteristic skin lesions of erythema nodosum.
19. Leukaemia or lymphoma with characteristic cells in the peripheral blood, bone marrow, or tissues.

Discussion.—Dr. Arthur W. Bagnall (Vancouver, B.C.): This is a most excellent effort, although it seems unlikely that everyone will ever agree completely on one set of criteria. However, there is just one point I should like to inquire about and that is the pronunciation that “Any interval free of joint symptoms may not be more than 3 months”. I wonder if that is wise. I have a private practice and clinic practice as well, and I am accustomed to seeing in my consulting room quite a few cases of undoubted rheumatoid arthritis who have a history of periods of freedom from joint involvement for much more than 3 months. This is what I call the “schnorkel” type of rheumatoid disease, because it only comes to the surface every now and then.

Dr. Ropes: This question indicates how hard it is to express the criteria. We think any interval between the two individual involved joints should not be more than 3 months. Surely, there may be an interval free from all symptoms, and then episodes of joint involvement. However, if it was our feeling that, if a patient had traumatic arthritis for one year, and 8 months later a second joint was involved and had at that time just enough other evidence to include him in the category of rheumatoid arthritis, it would be unwise to regard those two joints, in which the onset was separated by 8 to 12 months, as two joints involved in the disease. The criterion should obviously be re-worded.

* * *

Panel Discussion

Pathogenesis, Diagnosis, and Treatment of Gout
(Moderator: Dr. Alexander Gutman)

MODERATOR GUTMAN: I have asked Dr. Stetten to cover questions dealing with the intermediary metabolism or formation of uric acid and/or other purines.
Coming to the details of management, Dr. Charley Smyth will discuss acute gouty arthritis, and Dr. Elmer Bartels will consider the vexing problems of the prevention and treatment of chronic gouty arthritis.

Each panelist will present his particular subject, and this will be followed by a discussion of larger questions which are controversial or confusing. I shall refer to your specific questions that we have at hand, and that I hope will come to us in the course of this discussion.

(1) Current Status of Purine Biosynthesis—An Interim Report. By DeWitt Stetten, Jr., Bethesda, Md: As a result of the efforts of a large number of investigators working in various laboratories, considerable advances have been recorded in the understanding of the biosynthesis and metabolism of purines in the past few years. No attempt will be made here either to review the literature or evaluate the contributions from these many sources. Rather I shall attempt very briefly to integrate the various reported reactions, and to give a picture of how the purine nucleus is assembled, and what may happen to it in the animal body.

We may start our considerations with 5-phosphoribosyl pyrophosphate (Kornberg, Lieberman, and Simms, 1954). In this molecule, the anomic carbon atom 1 is activated by the pyrophosphate group which, in the presence of glutamine, is replaced by an amino group (Goldthwait, 1956), as shown in Fig. 1.

5-phosphoribosylamine is thus produced with glutamic acid and pyrophosphate as by-products. Glycine now reacts with phosphoribosylamine to give glycinamide ribotide (Goldthwait, Greenberg, and Peabody, 1955), as shown in Fig. 2.

Energy for this process is supplied by adenosine triphosphate.

Glycinamide ribotide is next formulated on its alpha nitrogen atom, the one-carbon addend arising from the beta carbon atom of serine, transfer being effected by some derivative of folic acid (Warren and Flaks, 1956), as shown in Fig. 3.

![Fig. 3.](image)

5-aminoimidazole ribotide now acquires a carbon atom at position 4, arising from bicarbonate, to which a nitrogen atom, derived from aspartate, is next attached (Lukens and Buchanan, 1956), see Fig. 5.

The product of these additions, aminoimidazole-carboxamide ribotide now adds a one-carbon fragment, a reaction again requiring the presence of a folic acid derivative. It is noteworthy that the initial inroad into this entire sequence was made when aminoimidazole-carboxamide was isolated (Stetten and Fox, 1945) and identified (Shive, Ackermann, Gordon, Getzenderan, and Eakin, 1947) as a product of micro-organisms whose folic acid production was inhibited by sulphonamides. The final step, closure of the six-membered pyrimidine...
ring, yields hypoxanthine ribotide (HxRP) which is identical with inosinic acid (Fig. 6).

![Fig. 6](image)

A summary of these several steps whereby the purine nucleus is assembled is given in Fig. 7. Here all irrelevant information is deleted and consideration is given only to the sequence of the successive additions of the atoms to form the condensed ring system of the purines.

![Fig. 7](image)

Inosinic acid (HxRP) has several fates available to it. From the point of view of the defect in gout, perhaps the most interesting one is lysis to the free purine, hypoxanthine (Hx), followed by two oxidative steps, both catalysed by xanthine oxidase. The successive products are xanthine (X) and uric acid (UA), see Fig. 8.

![Fig. 8](image)

In man, the process has been pictured as stopping here, although the occurrence of further breakdown of uric acid, uricolyis, has been established as occurring to a minor degree in normal man (Wyngaarden and Stetten, 1953).

Inosinic acid also serves as a precursor to the other purine nucleotides which occur as such as and as polynucleotides, nucleic acids, in the body. On the one hand, inosinic acid may be oxidized to xanthic acid (XRP), which is animated by glutamine, in the presence of adenosine triphosphate (ATP) to yield guanylic acid (GRP). On the other hand, inosinic acid may be aminated directly by aspartate, in the presence of guanosine triphosphate (GTP) to yield adenylic acid (ARP). Thus the two purine nucleotide types which occur in ribose nucleic acids arise from a common precursor.

The biosynthesis of polynucleotides is currently believed to stem from the ribose pyrophosphate derivatives of these two purines and the analogous pyrimidine derivatives, by the action of a recently described polynucleotide phosphorylase (Grunberg-Manago, Ortiz, and Ochoa, 1955). In vitro studies suggest that the composition of the polynucleotide may be determined in part by the composition of the mixture of mononucleotides from which it is formed. If this proves to be the case, there is clearly an advantage to the organism in the regulation of the ratio of generation of adenine and guanine nucleotides. As will be seen from Fig. 8, an elegant regulatory mechanism seems to be built into the reactions involved. To make guanine nucleotides from hypoxanthine, adenosine triphosphate is required (Abrams and Bentley, 1955). To make adenine nucleotides from the same precursor, guanosine triphosphate is required (Lieberman, 1956). Because of this curious cross-linkage of feedbacks, if, for any reason, production of GRP is limited, a limitation in ARP production would be anticipated to ensue, and vice versa. Likewise an overproduction of GRP might be expected to result in an increase in rate of generation of the ARP, and vice versa. Thus, at a chemical level there exists a novel kind of homeostasis wherein, not the abundance of a substance, but rather the ratio of abundances of a pair of products tends to remain constant.

REFERENCES

(2) Acute Gouty Arthritis. By Charley J. Smyth (Denver, Colo): My remarks will be directed first to agents useful in the treatment of acute attacks of gouty arthritis, and second, to the measures that are effective in the prevention of acute attacks.

Agents useful in the treatment of acute gout are colchicine, desacetylmycolchicine (Colcemide), phenylbutazone, and the steroid hormones. Oral colchicine is still the proven, dependable, safe, and almost uniformly effective agent and is generally accepted as the "standard" in the control of acute attacks. In most instances, it is still the drug of choice. Recently, intravenous colchicine has been reported on favourably. Single doses of from 0.25 to 6 mg. in 3 to 10 ml. normal saline have been found safe, rapid, and effective. The advantage of this route is the absence of gastro-intestinal toxicity, and it is especially suitable for post-operative attacks.

Desacetylmycolchicine, a new alkaloid derived from Colchicum autumnale, is reported to be as effective as colchicine and to be without toxic effects. If these early reports are confirmed, this drug will have distinct advantages over colchicine, but many more clinical studies need to be done.

Phenylbutazone has proved to be dramatically effective in acute gout. In fifty consecutive patients with 65 acute attacks of gout, its use resulted in prompt relief of joint pain, followed within 24 to 48 hours by control of other signs of inflammation. The following oral programme has been adopted:

1. A single large initial dose of 400 to 800 mg.;
2. Two doses of 200 mg. each at 2- to 4-hour intervals;
3. 300 to 400 mg. in divided doses during the next 2 to 3 days until all signs of joint inflammation have disappeared.

In this study, no toxic results occurred. Just how great is the risk of this drug in acute gout remains an unsettled question.

Cortisone, hydrocortisone, and corticotropin have all been shown to control acute attacks. The results are not uniformly good and therefore their use is reserved to instances where the above agents prove ineffective.

For the prevention of acute attacks, treatment must be continued indefinitely, and success depends upon the patient's willingness to submit to uninterrupted life-time therapy. Measures of proved value include:

1. Reduction of activity to avoid unusual trauma to joints;
2. Avoidance of foods known to initiate acute gouty episodes;
3. Avoidance of drugs known to trigger acute attacks, such as liver extract, mercurial diuretics, insulin, ergotamine, etc.;
4. Probenecid (Benemid) as continuous therapy in amounts adequate to keep the serum urate at a normal value.

The following additional measures are also useful:

1. Daily colchicine in low doses of 1 to 2 mg.;
2. Long-term sodium salicylates in high doses (90 gr. daily);
3. Abstinence from alcohol.

The place of phenylbutazone in long-term low-dose therapy (200 to 300 mg.), is not yet established as effective and safe.

(3) Prevention and Treatment of Chronic Gouty Arthritis, with special reference to Benemid. By Elmer C. Bartels (Boston, Mass.): The prevention of chronic gouty arthritis encompasses a programme of treatment aimed at forestalling the recurring acute attacks of gout which usually lead to gouty arthritis. There is, of course, the occasional patient with recurring gout, who does not develop chronic gouty arthritis even after 20 or 30 years.

The treatment of chronic gouty arthritis has two aims:

1. Prevention of recurring acute gouty arthritis;
2. Reversal of the late manifestations of gout, i.e. absorption of tophi and relief of bone damage.

Improvement in renal changes resulting from urate deposits, secondary pyelonephritis, and nephrosclerosis is desirable. Improvement in renal function with treatment has been reported, and clinical experience with present-day methods indicates that in most patients with gout the above aims can be met, at least in part.

If properly treated, gout can be controlled (not cured) with rare exceptions. To be successful, the treatment of gout must be highly individualized, as is the therapy of diabetes, since there are wide gradations of this disease.

The method of treatment to be instituted depends on many factors, such as frequency of attacks, duration of attacks, the presence of tophaceous gout, and possibly the presence of hyperuricaemia (uricacidemia) without gout, or so-called familial gout. If a patient has a mild attack every 1 to 2 years which responds promptly to colchicine, he may choose to continue this programme. The presence of tophaceous gout necessitates energetic maintenance treatment to avoid further progress of the disease with resulting deposits of urates. The question whether asymptomatic hyperuricaemia is harmful has not as yet been resolved. If it is associated with renal stones, the patient needs treatment—diet, administration of Benemid, and alkalization of the urine. The essentials of anti-gout maintenance therapy include:

1. A low purine and low fat diet;
2. No alcohol intake;
3. The use of a uricosuric agent.

Effective uricosuric agents include Benemid, which is preferred at present since it is well tolerated (the incidence of sensitivity reactions is 1 to 2 per cent.); sodium salicylate in 90 gr. daily doses (highly uricosuric, and not well tolerated because of side-effects); Butazolidin (G-72561), a new derivative said to be low in toxicity; Tromexan which has uricosuric properties similar to those of Benemid in dosages far below those required for anticoagulation. It appears that all the uricosuric drugs are potentiated by alkalization of the urine, this is especially true of salicylates.

The major goal of anti-gout therapy is a sustained normal level of serum uric acid. If this is accomplished over a prolonged period of time, the gout may be controlled. The dose of a uricosuric agent such as Benemid may vary from 250 to 3,000 mg. daily.
Gout is amenable to control by individualized maintenance therapy. The benefits of proper treatment are manifested by relief of attacks, the return of the serum uric acid level to normal, reduction in the size of existing tophi, healing of draining tophi, and reversal of bone changes.

Discussion.—Moderator Gutman: A good many queries that came to us dealt with the matter of diet. This has been touched upon already, but I think it might be helpful to review the situation, to crystallize the thinking of the panel. Dr. Stetten, would you present the case for diet from the metabolic point of view?

Dr. Stetten: Two aspects of this disease are seemingly only remotely related: the colchicine-responsive recurrent arthritis and arthralgia, on the one hand, and the increase in quantity of urate in the body, reflected by ultimate deposit of tophi, on the other.

At present I believe none of us has a clear idea how these two phases of the disease may be related, and there are some, perhaps, who suspect that this relationship may be very remote.

As far as I am aware, diet comes into consideration only in regard to the second of these two defects. The best reference that we have devised so far, to consider the possible effects of diet, relates to a mathematical quantity that we have termed the miscible pool of uric acid.

This may be simply defined as that quantity of uric acid in the body of a man capable of mixing promptly with injected uric acid. It is a concept analogous to the more familiar body space concept of the physiologist. This pool of uric acid, which is of the order of 1 g. uric acid in normal man, expands enormously in gout. It has been observed to expand in every gouty subject, so far as I am aware, who has been studied by this method. It has sometimes been observed to expand in the face of an apparently normal serum uric acid concentration.

The effects of diet anticipated are that, if the purine content of the diet is kept low, this contribution to the miscible pool at least can be eliminated. It is quite easy to secure a diet which is virtually devoid of purine. Most vegetables are practically devoid of them, eggs are very low, and milk is poor in them.

Some years ago our group collaborated with Dr. Gutman's group in a study of the effect of the protein content of the diet upon the amount of the miscible pool of uric acid. We concluded that the quantity of urate produced from dietary amino acid was enhanced when the protein content of the diet was increased.

On the basis of these findings, to reduce the miscible pool of uric acid, one would keep the protein content of the diet within reasonable bounds.

Dr. Bartels: We advise our patients to keep their diet low in purine and fat, and to avoid the use of alcohol.

Some patients who have very mild gout, on that plan alone, might be able to avoid trouble, but we have had patients who were under control on Benemid, with normal uric acid levels, who used alcohol to excess and followed no diet restrictions whatever and still maintained control. I do not suggest that as a means of treatment, but some patients neglect what we tell them, yet we are still bound to try to treat them.

Moderator Gutman: You see, there is still a good deal of difference of opinion in regard to the place of dietary regulation in the management of gout, although perhaps not as much as one might expect. Our own point of view in respect to diet is to distinguish the objectives of restriction, whether for prevention of the recurrence of acute gouty arthritis, or whether for retarding the development of chronic gouty arthritis.

I think there is every reason to believe, from metabolic considerations, that the more purine and protein and fat are consumed, the more uric acid is formed and retained in the body. Although we cannot measure this on a day-to-day basis, it is reasonable to believe that excesses in these food components will accelerate the rate of tophaceous deposit.

In respect to acute gouty arthritis, my experience is like that of the others. We find that there are important differences among patients, which cannot be predicted from any clinical or laboratory study, except by careful history taking, and we adjust dietary restriction to the individual requirements of the particular patient. Some gouty subjects can eat and drink almost anything they wish, without any apparent detriment, and we allow them a reasonably free choice in diet. In those in whom restriction seems important, as judged by their own experience, we attempt to restrict the diet and alcohol intake.

Dietary regulation for prevention of the recurrence of acute attacks is, then, empirical, the underlying mechanism not being clear.

This question bears on the prophylactic use of colchicine; it is so important in the practical management of gout that I hope you will permit me to review our own experience in this regard, as recently compiled by Dr. Yü.

We have given 112 gouty subjects with a prior history of multiple acute attacks a prophylactic colchicine regimen in doses varying from 0.5 to 1.5 mg. daily by mouth, the dosage being adjusted to individual requirements by trial and error.

Of these 112 gouty patients, 31 received daily prophylactic colchicine for from 5 to 10 years; 44 for 3 to 5 years; 28 for 1½ to 3 years, and nine for 1 to 1½ years. These are long-term statistics, because a judgment based on short-term observations cannot be of much value, in view of the unpredictability of the acute attacks.

Evaluation in thirteen of our 112 patients was difficult because of the irregularity of previous attacks; of the remaining 99, 67 were virtually symptom-free during the period of observation.

In thirty cases, attacks were satisfactorily reduced in number and severity, but control was less complete. Prophylaxis in the two remaining cases was unsatisfactory. No significant toxicity or intolerance was noted in this series.

We have been interested, also, in the question of the usefulness of Benemid as a prophylactic in acute gouty arthritis. Of the 67 patients showing excellent results, 28 were tophaceous and received Benemid regularly, and 21 had little or no tophaceous deposit and received colchicine only. We found no significant difference in the recurrence of acute attacks between the patients who received Benemid plus colchicine, and those who received colchicine alone.

In 27 patients who took colchicine and Benemid regularly but then discontinued Benemid, no definite effect was observed on the recurrence of acute gouty arthritis. On the other hand, nine patients who discontinued colchicine had a recurrence of acute gouty arthritis sooner or later.

Colchicine is valuable in preventing the recurrence of acute gouty arthritis. It may not prevent recurrences altogether, but it reduces the incidence and severity of the attacks, if the dosage is sufficient and the diet appropriately regulated.

Combining Benemid with colchicine is, I think, advantageous in patients with extensive chronic gouty arthritis.
but I doubt whether the administration of Benemid alone to patients without chronic involvement is of much value in preventing the recurrence of acute gouty arthritis.

**DR. BARTELS:** This list of patients is, perhaps, the longest and most carefully controlled of any group with which I am familiar, in which daily oral colchicine has been used as a prophylaxis. I think any additional studies would be welcome.

**MODERATOR GUTMAN:** A question directed to Dr. Smyth:
There has been a good deal of discussion and confusion about the use of phenylbutazone as a uricosuric agent. Is it or is it not uricosuric, and should it be used as a uricosuric agent?

**DR. SMYTH:** If you give enough phenylbutazone to raise the blood level to somewhere between 10 and 11 mg. per cent., the drug is usually uricosuric.

We wondered whether it had any promise as a chronic urate diuretic, or any prophylactic value. As an experimental study we have now followed seven patients for from 59 to 313 days of continuous therapy with 300 to 400 mg./day. None had an acute attack of gout, but there was no consistent lowering of the serum urate. Since we have much safer uricosuric drugs, Benemid and sodium salicylate, there is no reason to run the risk of long-term phenylbutazone therapy. I would not recommend it as a therapeutic measure for chronic gouty arthritis.

**MODERATOR GUTMAN:** This next question concerns the management of the gouty subject who has chronic gouty arthritis but also has some indication of renal damage.

**DR. BARTELS:** Is the presence of renal damage a contraindication to the use of uricosuric agents? I wish you would also comment, as you did in your prepared discussion, on the precise management of a case in which there is a history of renal colic due to the formation of calculi.

**DR. BARTELS:** It is recognized that a fair percentage of older patients, particularly those with tophaceous gout, do have evidence of renal disease. It was initially felt that Benemid should not be given to patients with a high degree of nitrogen retention. On the other hand, this is the type of patient who needs particular care, and, if it is possible to reverse his renal disease, we can be of great help to him.

We have had several patients with high degrees of nitrogen retention who developed anaemia, and tolerated Benemid very well. It is very difficult to produce such uricosuric effect or to lower the serum uric acid substantially. There is certainly no objection to the use of Benemid, and they tolerate it perfectly.

As regards renal calculi, I see no reason why their presence should preclude the use of Benemid, nor have I seen a higher incidence of stone formation in patients who are given Benemid.

It is true that in patients with a history of renal calculi it seems advisable to alkalize the urine, but we do not do this as a routine measure.

**MODERATOR GUTMAN:** There are some questions about secondary gout, of which you have heard a good deal in recent years. There is an increased incidence of gout in association with certain haematopoietic disorders, notably myeloid metaplasia, primary polycythaemia, and rarely also the leukaemias and haemolytic anaemias.

The management of secondary gout which presents as both acute and chronic gouty arthritis with extensive tophi, is always a difficult matter, but the general principles of therapy applicable in primary gout may be followed. The acute attacks respond to colchicine, ACTH, and phenylbutazone, and we use uricosuric agents such as Benemid in the prevention and treatment of tophaceous deposits.

In such cases, treatment is always difficult because of the underlying disease. Sometimes treatment of the underlying leukaemia or polycythaemia may precipitate acute gouty attacks which are very difficult to avoid in such circumstances.

Another question asks: What is the current status of the newer uricosuric agents compared with probenecid?

This refers to certain derivatives of phenylbutazone such as G-25671, which have marked uricosuric potency. I agree with Dr. Bartels and Dr. Smyth that these drugs are still very much in the experimental stage. We now have preparations that are powerful uricosuric agents and have some limited anti-inflammatory activity, but they require more extensive experimental work before they can be made available for general use.

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**PANEL DISCUSSION**

**Teaching Collection of Lantern Slides on the Pathology of Arthritis and Rheumatism**

**Introduction:** CURRIER MCEWEN, New York, N.Y.

**Subcommittee on Pathology of the Arthritis and Rheumatism Foundation:**
- LENT C. JOHNSON, Washington, D.C.
- J. PETER KULKA, Boston, Mass.
- LEON SOKOLOFF, Bethesda, Md.
- ROGER TERRY, Washington, D.C.

**Discussion:** D. MURRAY ANGEVINE, Madison, Wis.
- C. HOWARD HATCHER, Chicago, Ill.

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**PAPERS PRESENTED BY TITLE ONLY:**

**New Plan of Treatment of Low Back Pain.** By JOSEPH E. ALLEGRETTI, Chicago, Ill.

**Comparison of the Results of the Intra-Articular Use of Prednisolone Acetate with Hydrocortisone Acetate.** By ARTHUR W. BAGNALL, Vancouver, B.C., Canada.

**Occurrence of Multiple Fractures and Other Connective Tissue Alterations in Suckling Rats Injected with Beta-Aminopropionitril (Lathyrus Factor).** By JACKSON J. CLEMMONS and D. MURRAY ANGEVINE, Madison, Wisconsin.

**Rheumatoid Synovial Cyst of the Hip: Report of Three Cases.** MARK B. COVENTRY, ALLEN D. WEINER, and HOWARD F. POLLEY, Rochester, Minn.

**Results of a Simplified Sheep Cell Hemagglutination Test Using Mineral Acid for Precipitation of the Serum Eoglobulin Fraction.** H. WILLIAM CRAIG, GRACE P. KERBY, and ELBERT L. PERSONS, Durham, N.C.
Effect of Hydrocortisone and Growth Hormone on S35 Fixation in the Stomach of Hypophysectomized Rats. By Charles W. Denko, Chicago, Ill.


Disability Evaluation in Degenerative Arthritis. By Wm. N. Harsha, Oklahoma City, Okla.

Coincidence of the “Fibrosis Syndrome” with Degenerative Joint Disease in Peripheral Joints: A Survey of 300 Consecutive Admissions to an Arthritis Clinic. By Jed H. Irvine, New York, N.Y.

Role of Specific Rheumatological Skills and Other Disciplines in the Development of Musculoskeletal Nosology. By Jed H. Irvine, New York, N.Y.


Use of Cortisone and Renal Arteritis in Scleroderma. By Irving Leinwand, A. Wilbur Duryee, and Maurice N. Richter, New York, N.Y.


Effect of Prednisone and Prednisolone in Rheumatoid Arthritis: One Year Follow-up Study. By David H. Neustadt and Robert McClendon, Louisville, Ky.


Relation of Calcified Tendonitis to Cardiovascular Disease. By Joseph Ney, Washington, D.C.


Increased Capillary Fragility in Rheumatoid Arthritis. By Charles M. Plotz and Rubin Klein, Brooklyn, N.Y.


Peculiar Familial Form of Primary Systemic Amyloidosis. By Lawrence E. Shulman and Frederick C. Bartter, Baltimore and Bethesda, Md.


Observations on Long-Term Administration of Phenylbutazone in Musculoskeletal Disorders. By Otto Steinbrocker, New York, N.Y.


ANNALS OF THE RHEUMATIC DISEASES

Anti-Rh Antibody for demonstrating the Agglutination Activating Factor. By JOHN H. VAUGHAN and MARION V. WALLER, Richmond, Va.

Oral Colceminide in the Treatment of Acute Gout. By STANLEY L. WALLACE, JACOB COLSKY, and MORRIS BANOWITCH, Brooklyn, N.Y.

Comparison of the Metabolism of Hydrocortisone in the Normal and Rheumatoid Synovial Cavity. By HILDEGARD WILSON, RICHARD FAIRBANKS, CURRIER McEWEN, and MORRIS ZIFF, New York, N.Y.


Results of the Sensitized Sheep Cell Agglutination Test in Chronic Arthritic Diseases. MORRIS ZIFF, GEORGE FALLET, JOSEPH LOSPALLUTO, and CURRIER McEWEN, New York, N.Y.

Use of Hydrocortisone in the Treatment of the Painful Shoulder (Film). By A. W. BAGNALL, Vancouver, B.C. Canada.

HEBERDEN SOCIETY

At a Clinical Meeting held on October 19, 1956, at the Wellcome Foundation, the following papers were read:

DR. OSWALD SAVAGE (West London Hospital): A Study of the Course of Rheumatoid Arthritis during Continuous ACTH Administration with Clinical and Biochemical Observations. Preliminary findings were reported from a study of cases of active rheumatoid arthritis treated with ACTH in which the clinical assessment had been correlated with the erythrocyte sedimentation rate (Westergren) and the level of 17-hydroxycorticoid output in the urine measured by Norjemerski's method. These estimations were carried out by the Biochemical Department, West London Hospital, with the aid of a grant from the Empire Rheumatism Council.

The principal clinical measurements had been the total tenderness to firm pressure as measured in three grades and divided by the number of joints involved, and the grip measured by a Baumanometer cuff rolled and placed in a specially designed cover. Control groups had been studied in patients under treatment with rest, with salicylates, and with gold. In these there had been no variation from the normal levels of 17-hydroxycorticosteroid excretion in the urine. A difference in the strength of different batches of ACTH used had been apparent and it has been found most practical to keep patients on the same batch.

The patients were admitted to hospital in the first instance and a base-line of daily 17-hydroxycortico
teroid excretion was obtained before treatment was started. While in hospital they were taught to inject themselves with ACTH subcutaneously and this had been found a practical procedure. Some patients had injected themselves daily for as long as 3 years without difficulty and without local inflammation.

The patients in this study had been given sufficient ACTH to suppress symptoms and the erythrocyte sedimentation rate and the level of 17-hydroxycortico
teroid output in urine had been measured regularly.

The clinical response of patients in this group had been satisfactory, but the pattern of response had varied. Clinical improvement had been accompanied in some cases by a wide variation in the level of 17-hydroxycorticosteroid output in the urine; others suppression of symptoms had been maintained only when the adrenal cortex was continuously stimulated; in a third group it had been found possible to withdraw ACTH without clinical relapse after adrenal stimulation with a good clinical response and a fall in the erythrocyte sedimentation rate.

This work was carried out with the aid of the Dorothea Mason Foundation, West London Hospital Medical School.

DR. A. J. POPERT (West London Hospital): Effects of Stress in Patients with Rheumatoid Arthritis during Adrenal Stimulation. Normal people, when subjected to stress, consistently showed an increased urinary excretion of 17 OHCS: two patients who underwent oophorectomy showed a typical crescendo rise with peak levels two or three times higher than normal on the day after operation.

By contrast, patients with rheumatoid arthritis who were under treatment with ACTH did not regularly show an increased excretion during periods of stress. For example, a man who had an antrostomy while receiving 30 units ACTH daily showed a sharp fall in excretion over the operative period, and a woman who suffered from a severe orbital infection while receiving 30 units ACTH daily showed a lower level of excretion during the whole period from onset to operation and recovery. A man receiving 40 units ACTH daily showed a steep increase in excretion on the first day of a series of gastro-intestinal haemorrhages; this was followed by a progressive fall as his condition deteriorated, and culminated in a very large increase in excretion during the days when death was approaching.

These results suggest that, while the production of adrenocortical hormones in response to stress may some-