

MEDICAL PROGRESS:**Rheumatoid Arthritis: A Review of Recent Literature**EDWARD W. BOLAND, M.D., *Los Angeles*

MUCH clinical and laboratory investigation continues in an attempt to solve some of the mysteries of rheumatoid arthritis, the great crippler among the rheumatic diseases. So voluminous is the literature of the past few years that only some of the more important contributions can be summarized herein. The subject of rheumatoid spondylitis is not included in the present review as it was discussed in a recent issue of this journal.⁷

RELATIVE INCIDENCE

Cases of rheumatoid arthritis make up approximately one-third of admissions to most large arthritis clinics. At the Mayo Clinic 35 per cent of about 4,500 "rheumatic cases" seen annually have this disease.⁶² The same relative incidence prevailed also at the United States Army's two special centers* for chronic rheumatic diseases.⁵⁹ At an Army General Hospital located on the West Coast, peripheral rheumatoid arthritis constituted 12.4 per cent of 450 consecutive admissions for arthritis and allied conditions (peripheral and spinal types combined constituted approximately 20 per cent.²) The relative incidence in British military hospitals was less; rheumatoid arthritis was diagnosed in only 1.85 per cent of 270 soldiers admitted for rheumatic diseases at one general hospital⁹² (incidence for peripheral and spinal types combined was 7 per cent), and at another it accounted for only 6 per cent of musculoskeletal disabilities.²⁷ The disease was a major cause for evacuation of American soldiers from North Africa; such cases outnumbered rheumatic fever, rheumatic heart disease and pulmonary tuberculosis as nonneuropsychiatric causes, and were exceeded only by cases of asthma, peptic ulcer and nonulcer dyspepsia.⁹⁵

CLINICAL DATA

Initial involvement of finger joints was more common in females (38 per cent) than in males (26 per cent) in a civilian series studied by Sclater.⁹³ Among soldiers, initial involvement occurred in the lower extremity joints in 70 per cent of cases;³ the metatarsophalangeal and interphalangeal joints of the feet were involved in 41 per cent of cases, while corresponding joints of the fingers were affected in only 10 per cent. Such figures suggest that joint trauma plays a role in initial localization.

So-called "atypical" cases of rheumatoid arthritis occur so frequently that it may rightly be questioned whether the clinical pattern of "insidious onset, slow progressive course and asymmetrical joint involvement" should be labeled as usual or typical. Ex-

amples of atypical onsets and atypical early clinical courses, as observed by Ropes and Bauer,⁸⁹ included: (1) asymmetrical involvement, often a monoarthritis, (2) sudden febrile onsets precipitated by acute infection and accompanied by skin rash and migratory joint involvement, (3) bouts of arthritis precipitated by respiratory or other infections and not followed by permanent articular residues, (4) febrile onsets resembling rheumatic fever, (5) transient swellings affecting one joint and then another, resembling the "palindromic syndrome," (6) onsets consisting of recurrent joint and muscle aching and stiffness with qualitative characteristics of so-called "primary fibrositis." Most patients with "chronic synovitis" and "intermittent hydroarthrosis" eventually turn out to have rheumatoid arthritis.⁵⁰

Effect of Hepatitis:

Patients with rheumatoid arthritis who develop hepatitis or biliary obstruction of a degree sufficient to produce icterus usually experience either a partial or complete temporary remission of the disease. Subsidence of objective manifestations as well as subjective symptoms may be striking. Attempts made to imitate this phenomenon experimentally by injecting bile salts and bilirubin intravenously have failed. However, Gardner, Stewart and MacCallum⁴⁸ produced hepatitis experimentally by inoculating patients with icterogenic serum from patients with infective hepatitis and were able to study the phenomenon. Of 312 rheumatoid arthritis patients inoculated 32 developed jaundice. With the appearance of jaundice dramatic improvement was noted in 18 of the 32 patients (complete remission in ten, considerable improvement in eight); disappearance of pain and swelling was quickly followed by increase in range of motion. The production of hepatitis experimentally provides a means of evoking a remission under controlled conditions and an opportunity of analyzing the mechanism by which it is produced. How hepatic damage produces its curious ameliorative effect remains unknown.

Effect of Pregnancy:

Many females with rheumatoid arthritis experience relief during pregnancy; partial or complete remissions may occur, usually beginning at the end of the first trimester and persisting for varying periods after delivery. The mechanism in pregnancy, as in hepatitis, remains a mystery. Elevation of serum lipids, total cholesterol and phospholipids is common to both pregnancy and jaundice, but these fractions are not deficient in rheumatoid arthritis.^{14, 17}

* Army and Navy General Hospital, Hot Springs, Arkansas, and Ashburn General Hospital, McKinney, Texas.

Cardiac Findings:

Rheumatic carditis is a frequent autopsy finding in patients with rheumatoid arthritis but clinical or electrocardiographic evidence of cardiac involvement is not common.⁹¹ This disparity suggested to Hench⁶² that the pathologic lesions may be of such a type and degree as to be subclinical and not detectable before death. The occurrence of cardiac lesions at autopsy typical of rheumatic heart disease and the not infrequently observed clinical transition of apparent rheumatic fever into chronic rheumatoid arthritis have convinced some observers that the two diseases are closely related, if not the same disease with different predominant manifestations. Collins²⁴ suggested that rheumatoid arthritis may be a "lente" form of rheumatic fever, and Young and Schwedel¹¹⁶ believed that there was no fundamental purpose in separating the two diseases. However, Hench⁶² thought that the two diseases must be carefully distinguished and maintained that the finding of rheumatic heart lesions in patients with rheumatoid arthritis probably represented "the presence of two coincidental diseases."

PATHOLOGIC DATA

Rheumatoid arthritis is not solely a disease of the joints but a systemic disease characterized pathologically by widespread changes in various tissues and organs. Recent necropsy and biopsy studies emphasized those changes which occur in the heart, peripheral nerves and skeletal muscles.

Joints:

The pathologic changes were described by Keliian⁶⁷ as follows: Rheumatoid arthritis is an inflammatory reaction of the comparatively undifferentiated connective tissues. The relative vascularity of the synovial membrane and bone marrow favors the localization of circulating irritants, and in response to the offending agent there ensue hyperemia, edema, cellular infiltration, exudate and tissue proliferation. The synovial membrane becomes soggy, thickens (synovitis); from its loose areolar spaces tissue fluids seep into the joint cavity (hydrarthrosis). Later, finger-like processes of proliferated tissue project into the joint cavity (chronic villous synovitis). Granulations formed in the external layer of the synovial membrane may extend into the surrounding structures and cause them to contract (periartritic adhesions, contractures) or, more commonly, they may break through the barrier of the internal layer of the synovial membrane, creep over the articular cartilage (pannus), erode, and destroy it. Usually proliferative activity is going on in the marrow at the same time and the trabeculae of bone are thinned (atrophy). The cartilage is attacked and when the opposing cartilages are completely eaten away, the granulations contract to form adhesions (fibrous ankylosis); ultimately these connecting strands may ossify (bony ankylosis). Rheumatoid arthritis does not always run through this entire gamut of joint inflammation; it may proceed up to one or another phase and then arrest itself. If a

mechanical incongruity is created (eroded articular surfaces, over-distention, contractures, subluxation) the joint may in time break down architecturally. Joints with extensive synovial membrane and bulbous articular ends which contain a greater amount of marrow tissue are more likely to be affected by rheumatoid arthritis; thus rheumatoid arthritis predilects the knees, the elbows, the metacarpophalangeal and proximal interphalangeal joints.

Peripheral Nerves:

Widespread involvement of the peripheral nervous system in patients with rheumatoid arthritis was described by Freund, Steiner, Leichtentritt and Price.^{43,44} Lesions consisting of perineural nodules (nodular perineuritis) were found irregularly distributed, not only in the nerves of the extremities but also in peripheral nerves without joint distribution. Histologically the nodules consisted of an outer zone of lymphocytes with scattered plasma cells and an inner zone of polyhedral shaped cells having large irregular nuclei. Neuritic pains, paresthesias and trophic changes, common to the disease, might be attributed to such lesions.

Muscles:

Steiner, Freund, Leichtentritt and Price⁴² described also a nodular polymyositis consisting of compact accumulations of lymphocytes, a few plasma cells and occasional epithelioid and eosinophilic cells in specimens from 15 cases of rheumatoid arthritis. The disseminated nodules were found in biopsies taken at random (gastrocnemius, deltoid, pectoral, rectus abdominis, iliopsoas muscles, etc.). They were discovered in every case, and were considered as specific lesions. In 196 control cases no such lesions were found. Such a widespread myositis (together with coexisting nodular peripheral neuritis) offers an anatomic-pathologic basis for the muscle atrophy of rheumatoid arthritis which heretofore could not be explained on the basis of disuse alone.

Heart:

In a total of 152 recently reported necropsies on patients with rheumatoid arthritis, 59 (39 per cent) had cardiac lesions indistinguishable from those of rheumatic fever. Baggenstoss and Rosenberg¹⁰ demonstrated lesions typical of rheumatic heart disease in 16 (53 per cent) of 30 patients. Gross changes were present in the mitral valve in ten, in the aortic valve in six, in the tricuspid valve in two, and in the pericardium in six. Although pathologically identical, the lesions were considered less severe and less widespread than in rheumatic fever.¹¹ This frequent association of rheumatic heart disease and rheumatoid arthritis was verified by the necropsy findings of Fingerman and Andrus³⁷ (19 of 61 cases), of Bayles¹⁵ (6 of 23 cases), and of Young and Schwedel¹¹⁶ (24 of 38 cases).

LABORATORY DATA

Blood Counts:

Approximately three-fourths of patients with rheumatoid arthritis have hemoglobin values below 80 per cent, according to Haden.⁵⁴ Robinson⁸⁶ believes

that the anemia is partially due to simple plasma dilution (hydremia effect caused by a rise in plasma proteins) similar to that which occurs in pregnancy. The leukocyte picture is not characteristic; a mild leukopenia is frequent but occasionally a mild polymorphonuclear leukocytosis occurs. The differential count is rarely altered.

Erythrocyte Sedimentation Rate:

This test is generally accepted by most clinicians as a most useful index of disease activity. But 50 per cent of Short's⁹⁵ early or mild cases had normal rates, and Steinberg and Lowenstein¹⁰⁸ observed patients with hot swollen joints whose rates were normal and patients with clinically inactive disease whose rates were increased. Some investigators believe that a careful clinical evaluation is more dependable than the sedimentation rate both in diagnosis and in following the course of the disease.

Roentgenographic Findings:

Roentgenographic abnormalities (aside from periarticular soft tissue swelling) result from destruction of articular cartilage and from alterations in subchondral bone. When the pathologic process is restricted to the synovial membrane, roentgenograms are negative. It may take months or years for the development of sufficient cartilaginous or osseous change to be recorded on roentgenograms; though pathologically involved, some joints may never show positive x-ray findings. These considerations explain the time interval which exists between the development of localizing physical signs and the appearance of roentgenographic changes.⁶ Only 25 per cent of Short's⁹⁵ patients, observed in an overseas general hospital, demonstrated x-ray changes, and these usually were confined to varying degrees of bone atrophy. A common mistake is to rule out rheumatoid arthritis on the basis of negative roentgenograms. Further, the roentgen alterations are not specific for rheumatoid arthritis, as many different forms of arthritis may exhibit the same basic alterations. Camp²⁰ recognized the roentgenologist's limitations in attempting to differentiate between the various types of arthritis: "The pathologic and x-ray response of joints in various diseases is too similar to permit dogmatic interpretation of the roentgenogram."

Miscellaneous Tests:

The Weltman reaction, a test based on the coagulation of serum proteins in the presence of an electrolyte (CaCl_2), was considered a sensitive indicator of activity in rheumatoid arthritis by Milles and Salt.⁷⁷ But others believed that the test did not reflect the severity of the clinical picture, and Kling⁷⁰ considered the erythrocyte sedimentation rate to be a more accurate guide. The Metzger test was considered valueless.⁵³

Biochemical tests on the cerebrospinal fluid were made by Ludwig, Short and Bauer⁷⁵ on 101 patients with rheumatoid arthritis. The only significant abnormalities noted were increased concentrations of

protein; concentrations of protein were increased (46 to 70 mgm.) in 6.8 per cent of 50 patients with only peripheral joint involvement, 47 to 105 mgm. in 28.6 per cent of 42 patients with rheumatoid spondylitis, and in 15.8 per cent of the total 101 patients.

ETIOLOGY AND PATHOGENESIS

Despite continued research the cause of rheumatoid arthritis remains unknown. All of the currently considered etiologic theories—infectious, metabolic, endocrine, circulatory, psychogenic—lack proof.

Infectious Factor:

Although many clinical features and some immunological findings suggest that infections play a role in the pathogenesis of rheumatoid arthritis, carefully conducted cultivations of the blood and joint fluid have failed to prove that the disease is an infectious process. Fraser²⁶ cultured the blood of 61 patients with rheumatoid arthritis in beef-heart infusion broth. No organisms of any kind were recovered in 58, and in the remaining three diphtheroid bacilli were isolated; streptococci were never recovered. In 61 controls, five positive cultures were obtained, streptococcus viridans in three and diphtheroid bacillus in two. Angevine, Rothbard and Cecil¹ could find no significant organisms in culturing blood, joint fluid, synovia or subcutaneous nodules.

Patients with rheumatoid arthritis had agglutination titers of 1:160 or higher for hemolytic streptococci more often (58 per cent) than did normal controls (14 per cent) or patients with osteoarthritis (28 per cent).³⁵ Titers for serum antistreptolysins in rheumatoid arthritis were not found to be characteristic, whereas, in rheumatic fever they were usually elevated. Davidson²⁹ pointed out that positive agglutinins, antistreptolysins, and skin tests with streptococcal antigens mean only that the patient has been infected with streptococci, not that the arthritis is due to this organism.

Circulatory Factor:

According to Naide and Comroe⁷⁸ the peripheral vascular responses of patients with rheumatoid arthritis follow a characteristic pattern: the basal vascular tone was found to be high and the peripheral vessels to be easily constricted. This perhaps accounts for the thin atrophic skin with cold clammy hands and feet, cutaneous pigmentation, causalgia, hyperesthesia, symptomatic improvement with vasodilating procedures, and perhaps for flare-ups of the disease after emotional upsets or exposure to cold. Rheumatoid arthritis victims were found to be a vasospastic group before the disease actually developed. Normally, high vascular tone is more common in women than men and is most marked in the fingers and toes; this may account for the sex incidence favoring females and the predilection for involvement of finger and toe joints. Steinbrocker and Samuels¹⁰⁹ made oscillometric readings and found that about 60 per cent showed signs of vasospastic arterial disturbance.

Metabolic Factor:

Block and Murrill¹⁶ found no deviations from normal in total sulfur, total nitrogen and amino acid contents of total serum proteins in rheumatoid arthritic patients. Such negative findings appear to invalidate any suggestion that an altered composition of total serum proteins in arthritic patients reflects disturbed sulfur metabolism. The total lipid, total cholesterol and phospholipid contents of the plasma were also found to be normal.¹⁷ A slight but definite negative calcium balance, probably indicative of increased rate of calcium metabolism, was found in each of nine cases of rheumatoid arthritis studied by Ropes, Rossmel and Bauer;⁹⁰ the calcium excretion rate varied directly with the degree of decalcification noted roentgenographically.

Endocrine Factor:

There is no conclusive evidence that an endocrine imbalance plays any role in the production of rheumatoid arthritis. The simultaneous occurrence of some endocrine dysfunction is no more frequent than can be explained by chance, according to Davidson.²⁹

Psychogenic Factor:

Opinions varied regarding the importance of psychogenic factors in the etiology, precipitation and clinical course of rheumatoid arthritis. Halliday⁵⁷ was convinced that emotional upsets were frequent precipitating causes of rheumatoid arthritis; a "definite upsetting event" was found antecedent to the onset in nine of twenty patients, and in seven emotional conflicts were thought to have provoked recurrences. In contrast, emotional disturbances were rarely related temporally to the onset in soldiers (1 of 100 cases), less often than other factors such as infections or physical exposure.³⁸

TREATMENT

Management of Foci:

The attitude toward focal infection has become more and more conservative. The majority of clinicians agree that only definite foci should be removed, and then with the view of improving general health rather than curing the disease. Only occasionally does a well developed rheumatoid arthritis show definite improvement following the removal of an obvious local infection; eradication of definite foci should be undertaken "with hope but without promise." Most agree that devitalized teeth with roentgenographic evidence of periapical abscesses should be extracted.^{9, 52, 115} But devitalized teeth showing no periapical rarefaction should be regarded more conservatively;³³ they should be checked roentgenographically at intervals, and before extraction is accomplished the risk of interfering with nutrition by removing necessary mastication surface should be weighed.⁹⁶ Recurrently inflamed tonsils probably should be removed for reasons of general health, but Slocumb and associates¹⁰⁹ reported definite clinical improvement from tonsillectomy in only 5 per cent of patients whose infected tonsils were the

only discoverable focus. Shuster⁹⁷ obtained improvement following sinus surgery in only three of twenty-four early cases (12 per cent) and in one of eighteen (6 per cent) advanced cases. The evidence is distinctly against the importance of the gallbladder, intestines, genito-urinary system and female pelvis as sites of focal infection in rheumatoid arthritis, according to Short and Bauer.⁹⁶

Rest:

Pemberton⁸⁰ believed that rest as a form of therapy was neglected by physicians; a survey showed that fewer than 11 per cent prescribed it. The majority agreed that "complete bed rest" was indicated only in severe, acute or febrile cases,^{46, 56, 58} and during later flare-ups accompanied by local heat and severe pain. For chronic cases a minimum prescription of rest should be ten hours at night and two separate periods of one hour during the day.⁸⁸ During such periods the affected joints should be placed in the best possible position to insure the maximum function should fixed deformity ultimately develop. Daily systematic passive and active exercises to prevent joint stiffness and muscle atrophy are of utmost importance; these should be gentle and non-weight-bearing during the more active stages.

Diet:

Because most patients show a weight loss, a high caloric diet complemented with adequate vitamins and minerals is usually indicated,^{98, 39} but there is no special food substance which should be eliminated or which is specifically required by patients with rheumatoid arthritis.

Vitamins:

There is no known antirheumatic vitamin. However, the daily requirement of vitamins may actually be greater in patients with rheumatoid arthritis than in normal individuals⁷¹ and the addition of extra vitamins as a "booster" to general health can be considered as good practice. The course of the disease evidently is not altered by saturating the patient with any one vitamin. Large doses of thiamine chloride,⁴⁶ ascorbic acid⁶⁹ or vitamin A⁴⁷ fail to influence the symptoms.

Vitamin D:

Because of enthusiastic lay advertising and publicity which "overemphasizes part truths and overlooks the rest of available information," high potency vitamin D therapy recently has been resurrected, and has become a popular treatment for "rheumatic conditions," including rheumatoid arthritis.⁹⁸ Vitamin D in large doses may accomplish reduction of pain in some patients with rheumatoid arthritis,⁹⁹ but little or no objective change is observed.^{47, 46} Reductions in erythrocyte sedimentation rates and alterations in the clinical course are rarely encountered. Although the majority of investigators believed this treatment to be of little or no value,^{111, 69, 66, 18} some^{104, 34, 73} still reported enthusiastic results.

Massive vitamin D therapy is not without danger.⁷¹

Signs of early toxicity include sweet taste, nausea, vomiting, polyuria, polydipsia and occipital headaches.⁹⁸ Severe renal damage due to deposition of calcium in the renal parenchyma with resultant azotemia, albuminuria and cylinduria may result if these symptoms are ignored; two such cases, one with accompanying extensive calcifications about joints, were reported.²⁹ Toxic reactions were said to be encountered less frequently with the electrically activated vaporized sterol (Whittier process) than with ultra-violet irradiated ergosterol (Steinbock process).¹⁰⁴

Analgesics:

Salicylates are the mainstay for relief and usually are as effective or more effective than others. Most patients can tolerate 40 to 60 grains of acetylsalicylic acid daily without any apparent injury.³² Acetphenetidine occasionally may be more effective. Codeine is rarely necessary and morphine should be studiously avoided because of the danger of drug addiction. Demerol given orally was effective in relieving pain in 62 per cent of patients with rheumatoid arthritis investigated by Batterman,¹³ but ambulatory patients often experienced unpleasant side reactions. Although less than for opium derivatives, an addiction liability exists and Demerol probably has little place in the treatment of rheumatoid arthritis.

Physical Therapy:

Proper home physiotherapy with the use of relatively simple apparatuses (radiant heat, contrast baths and douches, wet packs, paraffin baths, hot tub baths, etc.) is of utmost importance in the management of rheumatoid arthritis. Proper use of heat, massage, passive and active exercises can be taught to the patient or his family, and home physiotherapy is something which can be used every day of the year.⁸¹ An electric pad or cheap heat lamp used consistently is of more therapeutic value than elaborate machinery which is only occasionally available.⁷⁶ Light massage over the muscles aids in circulation and relaxation, but the joint itself should not be rubbed. Massage does not increase muscular strength; this can be brought about only by active exercises.⁸² In general, joint exercises should be started as soon as any degree of painless motion is possible. For an acutely swollen painful joint exercises should be delayed, but to wait too long favors development of permanent disability.¹⁰⁷ Exercises must be supervised and graduated; they should not be done too enthusiastically, and if increased pain persists for more than two hours after completion, exercise has been too vigorous;⁸⁸ "purposeless wiggling of joints" should be condemned.⁹⁸ Salicylates given beforehand may aid in accomplishing joint movement. Active muscle training such as muscle setting and resistant exercises are of extreme importance and should be instituted early. Movements involving extension rather than flexion should be encouraged. Hurt⁸⁴ gave the following principles for muscle building: for a poor muscle—exercise with gravity eliminated; for a fair muscle—exercise

against gravity or its equivalent; for a good muscle—exercise against gravity and graded resistance.

Chrysotherapy:

According to Dawson, Boots and Tyson³⁰ chrysotherapy offers greater promise than other forms of therapy, but they warned of its dangers and advocated its use only in the hands of careful clinicians. When carefully given, the good effects of gold salts far outweigh the risk involved.⁵⁸ In the experience of Smyth and Freyberg¹⁰² gold therapy is "valuable in many cases" but "not uniformly beneficial" and "its potential toxicity is a definite objection to general use." Several^{56,29,41,51,85,110} cautioned against relying on gold alone; chrysotherapy may be an important adjuvant but the patient should be given also the benefit of the general program included in a conservative regime. Extreme views were held by Key⁶⁹ who believed that chrysotherapy should be employed in "every case" of rheumatoid arthritis, and by Short⁹⁴ who concluded that "it carries a danger of toxicity too great for any but an indispensable drug."

Indications:

Until recently most physicians have restricted the use of gold salts to cases not amenable to more conservative measures. This practice is still adhered to by some;^{115,98,105,26} but others, because of better results obtained, have encouraged its use in early cases.^{102,110,58,22,56} Chances for complete remissions appear to be better if gold salts are employed early.²¹ Most agree, however, that chrysotherapy should be delayed for at least three to six months after the onset, or until the likelihood of a spontaneous remission seems remote. Gold salts should not be used in any rheumatic affliction other than rheumatoid arthritis, with the possible exception of psoriatic arthritis.^{51,26}

Contraindications:

Severe diabetes mellitus, disseminated lupus erythematosus, nephritis, ulcerative colitis, hepatic insufficiency, blood dyscrasias and hemorrhagic tendencies are generally accepted as contraindications. Allergy,⁷¹ pregnancy⁵¹ and history of exfoliative dermatitis²⁶ were also mentioned recently, but hypertension was not considered as a contraindication by Stengel.¹¹⁰

Preparations:

Those compounds most commonly used in the United States are listed in Table I.^{58,45,105}

Dosage:

Gold is the active principle and since the gold content is different in various compounds dosage must be figured in equivalent gold doses.⁴⁵ A favored treatment schedule with myochrysin (50 per cent gold) has been to inject increasing amounts of the salt, from 10 mgm. to 100 mgm. weekly, until a total of 1.0 to 1.5 grams has been given. Gold thioglucose (Solganal-B Oleosum) also contains 50 per cent gold, but is absorbed more readily, and in order to have

TABLE I.—Gold Preparations in Common Use

Chemical Name	Proprietary Name	Solubility in Water	Physical State	Gold Content Percent
Gold Sodium Thiosulphate	Sanochrysin	+	Aqueous solution	37
Gold Sodium Thiomalate	Myochrysin	+	Aqueous solution	50
Gold Calcium Thiomalate	Calcium aurothiomalate	—	Oil suspension	50
Gold Thioglucose	Solganal-B Oleosum	+	Oil suspension	50
Gold Thioglycolanilide	Lauron	—	Oil suspension	54

an equal amount of gold retained about 150 per cent of the dose for myochrysin is required.⁴⁶ Gold thiosulphate contains only 36 per cent of gold and proportionately larger doses are needed. Because fewer toxic reactions result with smaller weekly doses, most authorities now use doses not exceeding 50 mgm. per week.^{46, 58, 55, 112, 22} Freyberg found that weekly doses of 25 mgm. gave inferior results. Common practice has been to give one, two or more series or courses of gold salts (1000 to 2000 mgm. each) with rest periods of two to six months between courses. The frequency of relapses during rest intervals prompted Hall⁵⁵ to give a single course followed by maintenance doses of 50 to 100 mgm. once a month for six months or longer. This is now a popular plan of treatment and maintenance doses (once every three to four weeks) for periods of one to three years following an initial course are being given by some. With a newer insoluble preparation, gold thioglycolanilide (Lauron), claimed to be substantially less toxic, much larger doses were recommended^{87, 110} (initial doses of 25 mgm., then gradually increasing the weekly doses to as high as 300 mgm. and total dosages as great as 3,750 mgm.).

Mode of Action:

Despite extensive research during the past few years the mechanism of how, why and where gold salt therapy works is unknown.⁴⁵ The results of recent experimental work on the metabolism of gold salts will be reviewed elsewhere.⁶⁰

Results from Chrysotherapy:

Results from recent investigations varied widely but in general about 50 to 70 per cent of patients were reported as becoming symptom free or notably improved. Results are usually better when treatment is begun in the earlier stages of the disease, but many late cases respond favorably and some early cases may be refractory. Ragan and Tyson⁸⁴ have reported their results, based on a three to five year follow-up study as follows: Complete remissions in 13 per cent; improvement in 76 per cent; no improvement in 11 per cent. Other recently published results are summarized in Table II.

Toxic Reactions:

Unfortunately, toxic reactions provide a definite drawback to the universal use of gold compounds for rheumatoid arthritis. Such reactions include: dermatitis (mild rash to exfoliative type), ulcerative stomatitis, ulcerative colitis, hepatitis, thrombocytopenic purpura, agranulocytosis, aplastic anemia, bronchitis, etc. Usually they are not encountered until after several hundred milligrams of the drug have been given⁴⁶ but may occur after very small initial doses (20-30 mgm.), during a second or third series, or even weeks after treatment is completed.¹⁰⁶ Ten authors recently reported the percentage of toxic reactions in their cases; the average was 37.1 per cent, with percentages ranging from 8.2 to 61.0. The majority of these were minor and disappeared

TABLE II.—Recently Published Results of Chrysotherapy

Authors	Number Patients Treated	Arrested or Markedly Improved (Percent)	Moderately Improved (Percent)	Unimproved (Percent)	Preparation
Dawson, Boots & Tyson.....	100	51	48	15	Myochrysin
McCarty.....	36	78	Myochrysin
Logeheil & Hoffman.....	74	65	14.7	Gold sodium thiosulphate
Smyth & Freyberg.....	80	61	Myochrysin, gold sodium thiosulphate, gold sulfide
Short.....	31	19.1	Solganal-B & Myochrysin
Thompson & Wyatt.....	26	61.3	37.6	Myochrysin & gold sodium thiosulphate
Gardner.....	250	70-80	Solganal-B
Cecil, Kammerer & De Prume.....	197	66	20	14	Myochrysin, Solganal-B & gold sodium thiosulphate
Price & Leichtentritt.....	101	60	Myochrysin & Solganal-B
Ray.....	50	50	25	12	Calcium thiomalate
Graham & Fletcher.....	95	66	20	13	Myochrysin
Cohen & Dubbs.....	122	53	13	Solganal-B
Hartung.....	264	54	Myochrysin
Rawls, Gruskin, Ressa, Dworzan & Schreiber.....	100	53	21	14	Solganal-B
Fraser.....	57	42	21	18	Myochrysin
Robinson.....	200	50	25	Myochrysin
Stengel.....	30	56.6	23	10	Lauron
Furlong.....	16	62	13	25	Gold sodium thiosulphate
Winkler.....	32	46.9	Myochrysin

promptly upon discontinuance of the drug, serious reactions being encountered in not more than 5 to 10 per cent of cases treated.³⁰ A few fatal reactions have been reported recently; one from ulcerative enteritis,²² one from thrombocytopenic purpura,³⁰ one from multiple small cerebral hemorrhages.¹⁰⁶ The current mortality rate has been estimated to be between 0.38 and 0.43 per cent.⁶¹

Treatment of Toxic Reactions:

Agranulocytosis, a toxic reaction capable of causing death, may now be controlled with penicillin.⁵ Serious reactions including severe exfoliative dermatitis, thrombocytopenic purpura and agranulocytosis have responded favorably and rapidly to intramuscular injections of British Anti-Lewisite (BAL), according to recent reports.^{23, 74, 83} These preliminary reports give promise that BAL may prove to be an effective weapon against serious gold reactions.

General Conclusions on Chrysotherapy:

These were drawn by Hench:⁶¹ "The toxicity inherent in chrysotherapy makes it unsuitable for use by average practitioners without special experience. Gold salts are not constantly effective, are not specific, are at best a palliative and have not been proved to be a necessary adjunct to routine measures. A strong counterargument is that gold may well accomplish in six months or less what nature or general measures may take six years to accomplish. Surgeons and patients do not hesitate to accept the risks of cholecystectomy or hysterectomy to relieve symptoms much more bearable than those of progressive rheumatoid arthritis. Yet the mortality rates of such procedures are as great or several times greater than that of chrysotherapy. The use of gold salts seems entirely justified (1) in cases of progressive rheumatoid arthritis unrelieved by a reasonable but not too long a period of older and safer methods of treatment, (2) when the patient clearly understands and accepts the risk, and (3) when the physician is in a position to give the treatments with the necessary clinical and laboratory safeguards."

Artificial Hyperpyrexia:

Current opinion is that prolonged febrile reactions produced by the Kettering hypertherm or by electromagnetic induction are of little value in rheumatoid arthritis. Although occasionally transient symptomatic improvement may ensue, such improvement is seldom sustained.³⁶ Geiger⁴⁹ could see no advantage of artificial prolonged fever over typhoid vaccine reactions.

Roentgen Therapy:

The results of roentgen therapy in peripheral rheumatoid arthritis are disappointing when compared with the rather encouraging results of such treatment in rheumatoid spondylitis.¹⁰³ But local roentgen therapy (600 to 900 "r") to individual large joints which are persistently painful and resist other forms of treatment (such as boggy knees and painful re-

stricted shoulders) may, not infrequently, render significant relief.^{112, 68}

Kaplan⁶⁵ found radon ointment "absolutely ineffective and useless" because it had little penetrating power. Conclusions were that "to assume it can influence the underlying joints or bones is entirely erroneous."

Vaccines:

The trend is definitely away from the use of vaccines in the treatment of rheumatoid arthritis, even among some formerly enthusiastic supporters.⁴⁶ In general, "vaccines have made out a bad case for themselves,"³² and one author⁷⁹ believes them to be harmful because the patient is allowed to "drift into a hopeless and helpless condition when other measures might have been used successfully." But a few proponents still exist and they continue to publish good results. Such results appear to be about the same regardless of what vaccine is used; e. i., 75 per cent "definite improvement" with intravenous streptococcus vaccine,¹¹⁵ 80 per cent "marked improvement" with vaccines prepared from several strains of diphtheroids,¹⁹ varying degrees of improvement in 76 per cent with streptococcus-staphylococcus combined antigen.¹¹⁴ To rheumatologists who use accepted criteria for the diagnosis of rheumatoid arthritis, who use objective signs as well as subjective symptoms as standards for improvement, who are cognizant of the natural fluctuations in the clinical course of the disease, and who base results on controlled studies, such claims for vaccines appear extravagant indeed.

Antibiotics:

The two antibiotics now commonly used for various infections, penicillin and streptomycin, have been of no value in rheumatoid arthritis. Boland, Headley and Hench⁴ gave penicillin (daily doses from 120,000 to 320,000 Oxford units and total doses from 1,800,000 to 3,250,000 units) to ten soldiers with early but progressive rheumatoid arthritis and found the results to be negative. Seven of the ten cases showed no improvement, one patient was worse, one showed slight subjective but, no objective improvement, and one demonstrated moderate objective and subjective improvement in some, but not all, of the involved joints. Because of the capricious nature of rheumatoid arthritis, the improvement in these two cases was regarded as unrelated to the penicillin. Comroe's²⁵ results were the same; six patients treated for periods of two to four weeks received no benefit.

Antireticular Cytotoxic Serum:

The so-called "A.C.B. Serum" ("Russian serum") of Bogomoletz and Strazhesko was tried by Bach⁸ in 35 cases and by Freyberg⁶³ in 30 cases of rheumatoid arthritis. The results were essentially negative.

Sulfonamides:

These have proved useless.⁴

Sulfur:

There is no biochemical or metabolic indication of need for, or benefit from sulfur medication, according to Freyberg.⁴⁶ Treatment with sulfur preparations has been abandoned at most clinics.

Neostigmine (Prostigmine); Physostigmine:

Relaxation of muscle spasm, relief of pain and increased motion in 16 of 19 cases of rheumatoid arthritis was claimed by Trommer and Cohen¹¹³ with the use of neostigmine bromide given orally and/or subcutaneously. Later even better results were reported with physostigmine salicylate given subcutaneously. However, Balboni, Hollander and Kydd¹² were unable to substantiate Trommer and Cohen's results and concluded that "prostigmine induces no significant relaxation of muscle spasm in rheumatoid arthritis." At the 1946 meeting of the American Rheumatism Association several rheumatologists expressed disappointment with this type of treatment.⁶³

Orthopedic Measures:

Simple splints made of plaster aid greatly in preventing deformities and should be employed early while medical measures are being instituted. During acutely painful stages plaster molds are most useful but must be removed at least once daily to allow motion.^{58,112} Prolonged splinting to the point of marked muscle and bone atrophy was warned against.^{115,101} Flexion contractures of knees frequently may be corrected by a series of posterior plaster shells; traction and manipulation, wedging casts and forceful stretching are ineffective and often harmful.⁷⁵

The indications for various orthopedic procedures designed to correct flexion contractures of knees were outlined:^{72,31} manipulation under anesthesia for mild deformities due to capsular contractures without serious joint damage; posterior capsulotomy for resistant flexion contracture with little destruction of articular surfaces; osteotomy for fixations in bad position for weight bearing and with extensive destruction of joint surfaces; arthroplasty for stiff joints due to bony ankylosis; arthrodesis for severely destroyed joints with persistent pain on weight bearing in patients who must stand at work, where stability is more important than movement. Kuhns obtained good results from posterior capsulotomies in 40 per cent of cases, from osteotomy in 36 per cent and from arthroplasty in 10 per cent. Synovectomy is sometimes resorted to for persistently swollen boggy knees without extensive articular destruction but the results are variable. Ghormley and Cameron⁵⁰ reported excellent results from this procedure in only 15.6 per cent, some improvement in 40.6 per cent and poor results in 40.6 per cent of cases.

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