MEDICAL PROGRESS:

Recent Advances in Rheumatoid Arthritis

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BOTH the lay public and the medical profession are beginning to realize the importance of the rheumatic diseases as social and economic problems. Research has received great impetus, and information is now being obtained which should lead to a greater understanding of this group of crippling diseases. Summarized herein are some of the contributions relating to rheumatoid arthritis which have appeared in the literature during the past two or three years.

CLINICAL DATA

Rheumatoid arthritis is not a disease solely of the joints, but a generalized systemic disease in which the predominant clinical manifestations are noted in the musculoskeletal system.[6] Patients are often sick for months, perhaps years, before typical joint changes develop. During this time prodromal constitutional symptoms such as weakness, fatigue, anorexia, weight loss, anemia, numbness and tingling of the hands and feet, and other vasomotor symptoms may be present.[9, 56] The onset may be marked by no special provocative incident, but according to Cecil[9] the majority of patients suffer some immediately preceding unusual strain to the physical equilibrium. A detailed study of possible precipitating factors in 100 soldiers with rheumatoid arthritis was made by Finney, Boland and Hench.[2] In 42 some factor which could have acted as a "trigger" appeared to be temporally related to the onset. An infectious process preceded the onset in 21, physical exposure in 12, trauma to a joint in five, physical fatigue in two, psychic trauma in one, and a surgical operation in one.

Textbooks should include descriptions of cases with atypical onsets and courses, as well as descriptions of the usual clinical pattern, because "atypical" cases occur frequently and offer the greatest problems in differential diagnosis. Examples of atypical onsets cited by Ropes and Bauer[55] included: Asymmetrical joint involvement, often monarthritis; sudden febrile onsets precipitated by acute infection and accompanied by skin rash and migratory joint involvement; bouts of arthritis precipitated by respiratory or other infections and not followed by permanent articular residues; febrile onsets resembling "palindromic syndrome"; onsets consisting of recurrent joint and muscle aching and stiffness with qualitative characteristics of fibrositis. Hench[24] described what might be called "episodic rheumatoid arthritis" characterized by transient articular reactions of one or more joints with symptoms affecting individual joints for only a short time, sometimes a very few hours, days, or weeks.

Atypical rheumatoid arthritis, with acute onset, may easily be confused with rheumatic fever on preliminary examination.[14] Differentiation may be possible only after the clinical course of the process has been followed. If the articular manifestations respond to full doses of salicylates, 7.76 to 9.72 gm. (120 to 150 gr.) per day, if joint symptoms subside within a reasonable period of time without leaving anatomic or physiologic residues, and especially if clinical and electrocardiographic cardiac abnormalities are detected, a diagnosis of rheumatic fever is made. If, however, the response to salicylates is inadequate, if chronic arthritis persists or progresses after subsidence of the acute phase, and if clinical and electrocardiographic evidences of heart disease are lacking, a diagnosis of rheumatoid arthritis is made. Engleman[19] studied the clinical similarities and dissimilarities between a group of soldiers with rheumatic fever and a group with onsets simulating rheumatic fever, but who later developed atypical rheumatoid arthritis. He did not consider evidence of carditis as an accurate criterion for differentiation because in adult rheumatic fever carditis is not detectable in a significant number of cases.

Although cardiac lesions, indistinguishable pathologically from those caused by rheumatic fever, are found in a high percentage (26 to 65 per cent) of patients with rheumatoid arthritis at necropsy, clinical signs of heart disease are rarely met during life. This striking discrepancy has led to detailed cardiovascular studies in patients with rheumatoid arthritis. In one investigation the results of auscultatory examination, roentgenograms of cardiac contour, and electrocardiograms were approximately the same in 147 patients with rheumatoid arthritis as in 100 normal controls.[54]

It is not sufficiently understood that rheumatoid arthritis can be precipitated by a gonorrheal infection just as it can be precipitated by tonsillitis, influenza, or some other acute infection. Also, mild, intermittent, or quiescent rheumatoid arthritis can be aggravated by acute genital gonorrhea. Such cases have sometimes been called "post-gonorrheal rheumatoid arthritis" but this condition does not represent chronic rheumatoid arthritis engrafted on, or evolving from, a subsiding acute gonorrheal arthritis; it represents simply rheumatoid arthritis precipitated or aggravated by acute genital (not articular) gonorrhea.[27] Proved gonorrheal arthritis among American soldiers in World War II was rather rare. Hench and Boland saw many more cases of rheumatoid arthritis precipitated or aggravated by gonorrhea than of gonorrheal arthritis. Most of the former

cases were erroneously labeled gonorrheal arthritis, treated as such unsuccessfully by sulfonamides or penicillin or by fever therapy, and the patients transferred to the Army's rheumatism center with the notation that they had "gonorrheal arthritis resistant to penicillin and/or sulfonamides." In the experience of these investigators most cases of so-called "gonorrheal arthritis resistant to chemotherapy" have turned out to be cases of rheumatoid arthritis as shown by their subsequent course, therapeutic tests and, in some cases, articular biopsies.

Morrison, Short, Ludwig, and Schwab[42] did electromyelographic studies on 34 patients with rheumatoid arthritis. Whereas the muscles of normal individuals in a relaxed state show no electrical activity, patients with rheumatoid arthritis have an inconstant state of tension in muscles related to involved joints. Disordered muscle function preceded clinical evidence of articular disease in one patient. Spontaneous muscular activity is not peculiar to rheumatoid arthritis; it was found in two of four patients with arthritis due to specific infections, and in one with joint disability due to fixation. Similar patterns may be seen in poliomyelitis, infectious polyneuritis, and in nerve injuries. Blockage of the peripheral nerve was found to interrupt the path of origin of the motor discharges, but electromyelographic evidence of upper motor neuron involvement could not be demonstrated. Conclusions were that rheumatoid arthritis causes direct involvement of the neuromuscular system, and that spontaneous muscle activity may result from pathologic lesions in the lower motor neurons.

That hepatitis or biliary obstruction of sufficient severity to produce significant icterus may cause temporary partial or complete remission in patients with rheumatoid arthritis is now an accepted fact. Various attempts have been made to probe the mechanism by which such relief is obtained, but so far these have been futile. Intravenous injections of bile salts and of bilirubin have failed. Rennie and Fraser[50] inoculated ten volunteer rheumatoid arthritic patients with serum from patients who had acute infective hepatitis. Hepatitis developed in two of the patients, and both experienced dramatic subjective and objective improvement, the relief being greatest when icterus was maximum. Six months later one had relapsed partially and the other completely. The transmission of acute infective hepatitis should not be considered as a form of treatment for rheumatoid arthritis, but it could serve as a tool to alter the activity of the process, thereby allowing exploration of the mechanisms at play during remissions and exacerbations of the disease.

PATHOLOGY

The pathologic changes in rheumatoid arthritis are widespread throughout the body, involving a variety of organs and tissues. Inflammatory reactions are found in joints, capsular and pericapsular tissues, subcutaneous nodules, kidneys, heart, peripheral arteries, skeletal muscles, and peripheral nerves, and these are probably concomitant and coordinate lesions due to the same unknown cause.[59]

Joints. The primary lesion is in the synovial membrane, which becomes thickened by edema, hyperemia, and inflammatory cell infiltration. Varying degrees of effusion occur and hypertrophic villi appear in which there are collections of lymphoid cells. Contrary to the opinion of some observers, Flynn[66] believes that these collections of lymphocytes are not specific for rheumatoid arthritis but may be found in a number of other articular diseases. In severe cases a pannus forms which grows inward across the cartilage, gradually destroying it, and resulting in roughening and irregularity of the articular surface. Reparative changes follow the inflammatory stage and lead to ankylosis, which is first fibrous, but later may be calcific or bony.

Bones. Below the subchondral plate the marrow spaces are normally occupied by fibrofatty tissue. In severe rheumatoid arthritis granulation tissue occupies these spaces and its proliferation destroys the osseous trabeculae and the subchondral plate; hence the articular cartilage may be attacked on one side by pannus and on the other by granulation tissue in the marrow spaces.[66]

Subcutaneous Nodules. Microscopically the subcutaneous nodules of rheumatoid arthritis all have a similar structure consisting of connective tissue in which there are a number of granulomatous lesions. The granulomas are made up of a central area of necrosis surrounded by a zone of inflammatory cells (large monocytes) and then a zone of fibroblasts in palisade arrangement.[66]

Peripheral Nerves. Lesions in the peripheral nerves, similar to those described by Freund, Steiner, Leichtentritt and Price (1942) and others, were found in 26 of 31 cases studied at necropsy by Morrison, Short, Ludwig and Schwab.[42] Isolated and distinct inflammatory reactions, consisting of collections largely of lymphocytes and plasma cells with endothelial and occasional epithelioid cells or monocytes, were found widely scattered in nerve sheaths. Certain axonal reactions, or retrograde degenerations, were found in the corresponding nerve cell bodies (anterior horn cells or posterior ganglion cells). A few studies on ganglia of the sympathetic chain failed to exhibit conclusive findings. Nodular perineuritis may not be specific for rheumatoid arthritis, as similar lesions have been found in disseminated lupus and dermatomyositis.[66]

Central Nervous System. Morrison, Short, Ludwig, and Schwab[42] also made postmortem examinations of the central nervous system in 44 patients with rheumatoid arthritis and compared the findings with the necropsy findings in a control group of 50 with similar age distribution. No specific lesions were found in the brain or spinal cord in patients with rheumatoid arthritis, but alterations usually attributed to aging were more pronounced than they were in the controls.

Muscles. Steiner, Freund, Leichtentritt, and Maun[59] in 1946 extended their earlier observations of nodular polymyositis (microscopic focal accumulations of lymphocytes and plasma cells, occasional

mast cell, and rare polymorphonuclear or eosinophilic cell) in rheumatoid arthritis. These compact inflammatory lesions were found in nine additional cases of rheumatoid arthritis. In those cases the lesions were widely disseminated and were found in muscle biopsy specimens taken at randon. These observers and others[18] considered the lesions specific for rheumatoid arthritis, as similar lesions were not found in 196 control observations including examinations of muscle from patients with various nervous and muscle diseases. Clawson, Noble, and Lufkin,[11] however, have expressed doubt whether the muscle lesions can be considered as specific on a morphologic basis; whereas the nodules were found more frequently in patients with rheumatoid arthritis, they were found also in 118 of 450 routine autopsy cases (36.2 per cent) studied by them.

ETIOLOGY AND PATHOGENESIS

Truthfully and simply stated, the cause of rheumatoid arthritis is not known. Of the various hypotheses offered heretofore, the theory of infectious origin has had more indirect evidence for support than have others—but that theory has been insecure and has lacked proof. The presence of bacteria of any species has not been consistently demonstrated with rheumatoid arthritis.[21] Inflammation does not necessarily signify infection, as the signs and symptoms in gout or fresh burns bear witness. A rapid erythrocyte sedimentation rate does not necessarily indicate an infectious process, as increased rates are found in a number of established non-infectious diseases. Positive agglutinins, antistreptolysins, precipitins, and skin tests with streptococci antigens suggest only that the patient has been infected with streptococci, not that the arthritis is due to these organisms.

Recently Hench, Kendall, Slocumb and Polley[28] made a most important step toward solving the pathogenesis of rheumatoid arthritis. They were unable to harmonize the microbic theory with the phenomena of relief of the disease by pregnancy and jaundice. Further, they reasoned that certain procedures (general anesthesia, surgical operation, etc.) and states (pregnancy) which induced temporary remissions in rheumatoid arthritis were capable also of stimulating the adrenal cortices. Subsequently they discovered that a hormone of the adrenal cortex, cortisone (17-hydroxy-11-dehydrocorticosterone: Compound E), as well as pituitary adrenocorticotropic hormone (A.C.T.H.) exerted rapid and dramatic ameliorating effects when administered to patients with rheumatoid arthritis. Cortisone, or its synthetic acetate, or synthetic Compound E acetate (Cortisone), was administered intramuscularly in large doses (optimal doses of 100 mg. daily after an initial dose of 300 mg.) to 14 patients with severe or moderately severe rheumatoid arthritis. In each case pronounced improvement of the clinical features and sedimentation rates began to occur within a few days (usually two to four). When administration of the hormone was discontinued, relapse usually followed promptly. Essentially similar results, accompanied by various biochemical effects, were obtained from the administration of A.C.T.H. to two patients. The full importance of this discovery cannot yet be weighed, but its influence on future research will be great—perhaps it will serve as the key which will open the door to understanding of the pathogenesis of rheumatoid arthritis and related diseases.

TREATMENT

Management of Foci. A conservative attitude has become universal: Only definite foci should be eradicated, and then only with the view of bettering the general health, not for the purpose of directly curing the disease.[40, 49, 66] According to Freyberg,[21] two considerations should govern the management of foci of infection: "(1) Just as a patient without rheumatic disease should have abscessed teeth or infected tonsils removed, so should the patient with rheumatoid arthritis. (2) By removal of such infected tissues, the patient's general health might be improved and thereby his ability to combat the arthritis might be indirectly facilitated."

Vaccines. While most observers have abandoned the use of vaccines, a few adherents of vaccine therapy still exist. Key[34] makes the following pertinent query: Why should one expect a vaccine made of one or another organism to cure a disease of unknown etiology when there are numerous diseases of known etiology in none of which has any vaccine been found to be of benefit?

Foreign Proteins. Cecil[9] believes that febrile reactions produced by intravenous injections of triple typhoid vaccine have a definite but limited place in treatment. It is not recommended for chronic, well-established cases, but in initial stages, especially in subacute febrile patients, it will occasionally bring about rapid and complete cessation of symptoms.

Diet. There is no specific diet. Because most patients with rheumatoid arthritis are undernourished and underweight, every effort must be made to maintain nutrition at its highest point by a well balanced diet.[31, 46, 61, 62] To achieve this, a diet high in calories, high in vitamins, rich in fruits and vegetables[9] and with a normal ratio between protein, carbohydrate and fat is indicated.[39]

Vitamins. Supplementary vitamin therapy apparently is indicated because absorption of dietary vitamins is faulty in debilitated individuals.[55] But there is no specific vitamin for rheumatoid arthritis and vitamins at best play only a supportive role, their effect being tonic and in no way specific.[49, 63] Neither the symptoms nor the course of rheumatoid arthritis is altered directly by the administration of Vitamin A, Vitamin B complex (thiamine hydrochloride, niacin, riboflavin), Vitamins C, E, or K.[63]

Vitamin D. A few physicians still consider the use of concentrated doses of Vitamin D of some value; however, the majority of experienced rheumatologists not only regard it as essentially useless,[25, 46] but as potentially dangerous.[4, 5, 29] Traeger[63] concludes

that while some cases show definite slow subjective improvement, objective change is infrequent. Rawls,[49] after ten years' experience with Vitamin D, believes that "it is of little or no value regardless of the preparation used."

Transfusions; Hematonics. The hypochromic anemia associated with rheumatoid arthritis frequently does not respond adequately to iron salts. Often one or more blood transfusions will correct the anemia and start the patient on the road to improvement.[9, 31, 61] Stephens, Borden, Holbrook and Hill[60] found that the blood picture was improved in all of 20 patients with rheumatoid arthritis treated with folic acid for a period of three months. Usual dosage was 20 mg. daily, but larger doses up to 100 mg. daily were given if initial response was not adequate. Improvement consisted of increases in mean corpuscular volume, packed red cell volume, hemoglobin, and in color index, and improvement in the structure of the erythrocytes; but a comparable rise in the total erythrocyte or leukocyte counts did not occur.

Antibiotics: Penicillin, Streptomycin. Unfortunately these have proved ineffective.[6, 23, 31]

Antireticular Cytotoxic Serum (A.C.S.). Further experience with this serum substantiates Bach's conclusions (1945) that it is probably worthless in the treatment of rheumatoid arthritis.[46, 49, 52]

Neostigmine (Prostigmine): Physostigmine. Unsatisfactory results were obtained by Balboni, Hollander and Kydd[2] with both subcutaneous and oral prostigmine given to tolerance to 23 patients. In only two cases was there any appreciable decrease in muscle spasm, and in one of these the effect was inconsistent. Unpleasant and often alarming reactions occurred in 14 of the 23 cases. The conclusion was: "A potent drug such as prostigmine should yield much more definite benefit than we have observed in order to justify its continued use in rheumatoid arthritis." Rawls and associates used prostigmine in over 1,000 cases, and the number in which improvement was shown was "relatively small."[49]

Transfusions of Blood from Pregnant Women. Barsi[3] reported a "new treatment" suggested by the observation (made by Hench in 1938 and later by others) that the majority of females with rheumatoid arthritis have a temporary remission during pregnancy. He gave "several" transfusions of 300 cc. citrated blood from pregnant women to 28 patients with rheumatoid arthritis. Of these, 64 per cent recovered or improved and 36 per cent remained unchanged. Unfortunately this report has resulted in encouraging (and probably unwarranted) lay publicity in the press and on the radio. Barsi's statistical results are the same as those reported for many other forms of therapy—"the inevitable 60 to 70 per cent improved." Important details are missing in the six case abstracts presented and the criteria of improvement are not stated. Lacking is a controlled series treated by series of transfusions of blood from non-pregnant persons.

Curare. Schlesinger[66] believes that injections of curare in oil and beeswax are a useful adjunct in the treatment of patients with severe muscle spasm and reflex shortening of muscles. Curare relaxes the flexor protective mechanisms and allows better response to physiotherapy. In some cases of rheumatoid arthritis in which electrical activity is shown by electromyelographic studies, such activity subsides after administration of curare.

Analgesics. For relief of pain, no drug stands up so well as acetylsalicylic acid[9, 39] and as far as can be determined it does no harm.[66] There is no justification for giving salicylates intravenously.[16] Because of their habit liabilities, opiates and Demerol® are condemned.

Chrysotherapy. Despite long experience with gold compounds, their exact value in the treatment of rheumatoid arthritis has not been determined. Although diverse opinions exist, many experienced, careful rheumatologists maintain their conviction that chrysotherapy is the best single remedy now available for rheumatoid arthritis[9, 25] or the only remedy which will consistently change the course of the disease in a high percentage of cases.[66] According to Cecil these are not sensational statements, considering how disappointing most other remedies are. Hostility toward gold compounds has been occasioned by the relatively frequent toxic reactions which attend their use. However, the vicious nature of the disease attacked may justify the risks—big game cannot be fought successfully with small caliber weapons.[26]

1. *Indications.* Rheumatoid arthritis appears to be the only rheumatic disease in which the use of gold salts is justified.[15, 58] Not all patients should receive chrysotherapy; the physician should be convinced that the disease is active and progressive. Many believe that a reasonable trial on conservative measures should be given first. Some contend that gold salt therapy should be "a last resort," should be withheld until all other measures have failed. Others urge that chrysotherapy be instituted as early as possible, preferably within the first two years of the disease, rather than late after irreversible changes have taken place.

2. *Contraindications.* The generally accepted contraindications to chrysotherapy are: Severe diabetes mellitus, disseminated lupus erythematosus, nephritis, ulcerative colitis, hepatic damage, blood dyscrasias and hemorrhagic tendencies, pregnancy, and history of previous exfoliative dermatitis.[6, 12] Neither vascular hypertension nor chronic valvular heart disease is a contraindication.[10]

3. *Preparations.* Soluble compounds include gold thioglucose (Solganal-B Oleosum®), gold sodium thiomalate (Myochrysine®) and gold sodium thiosulfate (Sanocrysin®). Insoluble compounds include gold calcium thiomalate and gold thioglycolanilide (Lauron®).[6] Apparently gold must be combined with a sulfhydryl group to be effective,[66] but the gold content is believed to determine therapeutic activity.[58] The water-soluble compounds are more rap-

idly absorbed and appear to have some therapeutic advantages.[16, 58] The insoluble salt, gold calcium thiomalate, was considered slightly less toxic than the soluble salt, gold sodium thiomalate (Kersley).[32] Robinson[51] believes gold thioglycolanilide to be equally efficacious therapeutically and definitely less toxic than soluble salts, but others found its toxicity to be the same.[46] Colloidal gold preparations, such as colloidal gold sulfide (Aurol-Sulfide®), are rapidly phagocytized in reticuloendothelial cells, especially in the liver and spleen; hence, although intoxication is prevented, therapeutic effectiveness is minimal.[13, 16, 58]

4. *Dosage and Methods of Administration.* Formerly large individual doses (100 to 500 mg. of the salt) were given, but these were found to be dangerous because of the frequency and severity of the toxic reactions encountered. The trend recently has been toward smaller doses, not to exceed 50 mg. of a soluble gold compound having a metallic gold content of 50 per cent (25 mg. of metallic gold). The basic schedule now advocated by most authorities[8, 9, 25, 46, 58, 61] is as follows: First dose, 10 mg. intramuscularly; second dose, 25 mg.; third and succeeding doses, 50 mg. An interval of one week is usually allowed between doses. Some prefer to give individual doses of 25 mg. once a week. Whereas an arbitrary maximum dose may be adhered to, there should be no fixed amount. Dosage must be regulated somewhat according to the patient's reactions and the development of toxic symptoms.[32] In mild cases of the disease, and in those in which the patient is suspected of being susceptible to toxic reaction, individual doses of 25 mg. probably should not be exceeded.

Most observers agree that the total amount administered in a course should be between 750 and 1,500 mg. of a soluble salt (375 to 750 mg. of metallic gold). But according to Cecil[10] there should be no fixed amount because some patients improve rapidly and need comparatively small amounts, while others need larger doses. Ragan and Tyson[48] contend that if no response is obtained after 2,000 mg. has been given, further use of gold is futile.

Formerly the popular treatment schedule was to give one, two, or more courses of gold compounds with rest intervals of six weeks to six months between courses. The modern trend is to abandon multiple courses of treatment and to give a single course, followed thereafter by "maintenance doses" consisting of 50 mg. every two to four weeks for an indefinite period.[8, 10, 46, 58, 62, 66] Maintenance doses tend to reduce the frequency of relapses. If the multiple course schedule is adhered to, and if relapse occurs, it is important to resume chrysotherapy in small doses (5 or 10 mg. of the salt) in order to avoid toxic reactions.[10]

5. *Mode of Action.* The mode of action of gold compounds remains unknown. Short, Beckman and Bauer[58] reviewed the various hypothetical explanations: The serum of patients receiving gold salts has increased bacteriostatic powers against certain hemolytic streptococci, but since no bacterial cause for rheumatoid arthritis has been found, this observation does not furnish an explanation. That deposition of gold in reticuloendothelial cells might stimulate defense mechanisms of the body has been postulated. It has been suggested that the effect of gold may be mediated by the production of liver damage, but demonstrable toxic effects on this organ have been rare. No evidence has been presented that gold has an analgesic effect. Attempts have been made to find a common denominator for remissions associated with jaundice, pregnancy, and gold, but so far these have been unrewarding.

6. *Results.* Ragan and Tyson[48] studied the immediate response and the long-term results after three to four years in 142 patients treated with gold compounds (72 received gold sodium thiomalate; 19, gold calcium thiomalate; and 51, gold thioglucose). The immediate response after a single course of 0.5 gm. or more of the compound was as follows: Pronounced subjective improvement in 55 per cent; decided objective improvement in 50 per cent; no improvement in 11 per cent; definite but "not startling" improvement in the remainder. Thirteen per cent remained asymptomatic for 45 to 78 months after a single course, and 75 per cent had relapse. Seventy-seven of those who had relapse received a second course of treatment and 80 per cent of these again obtained improvement. In general terms, the results were summarized as follows: Of patients receiving full treatment with one or two courses, 10 to 20 per cent show no improvement, and 40 to 60 per cent show striking improvement; but 80 to 90 per cent will relapse within five years, and of these, 80 per cent will again be benefited by more gold.[46]

Less favorable results with the "course" method were reported by others. Short, Beckman, and Bauer[58] made a critical study of results in 35 patients treated with a single course of gold compounds and compared them with the results obtained in a group of 274 patients receiving only general and orthopedic treatment. Of the 35 patients receiving gold, 21 (60 per cent) obtained immediate improvement, but 13 later had relapse, giving a total net improvement in only eight cases (23 per cent). Better net results were obtained with general measures alone, 52.9 per cent of the patients showing improvement. The results of Browning, Rice, Lee and Baker[8] were similar.

Using the currently popular "maintenance dose" plan of therapy, Waine, Baker, and Mettier[65] compared the results in 58 patients with those in 62 control patients receiving general supportive treatment only. The patients obtaining gold compounds (gold sodium thiosulfate or gold sodium thioglucose) received average total doses amounting to 3,200 mg. (1,600 mg. in terms of the metal). Results were as follows: Arrested, 20.7 per cent; decidedly improved, 36.2 per cent; improved, 24.1 per cent; unimproved, 11 per cent. In the control group, the results were as follows: Arrested, 9.7 per cent; decidedly improved, 19.4 per cent; improved, 27.4 per cent; unimproved, 43.5 per cent. The conclusion drawn was: "Soluble gold salts are therapeutically

effective in peripheral rheumatoid arthritis, since the rate of significant improvement is approximately twice as high in the gold-treated series as in the controls."

7. *Toxic Reactions.* Most observers agree that about one patient in four experiences some untoward effect, for the most part of minor order. Ragan and Tyson[48] noted significant toxic reaction (pruritus, rash, stomatitis or blood dyscrasia lasting more than a month) in 39 per cent of patients receiving Myochrysine,® in 31 per cent of those receiving Solganal-B Oleosum,® and in 21 per cent of those receiving gold calcium thiomalate. Minor reactions, including skin rash, mouth sores, and transient albuminuria, develop in about 25 per cent of cases.[10] Serious reactions include exfoliative dermatitis, hepatitis, ulcerative enterocolitis, thrombocytopenic purpura, agranulocytosis, and encephalitis. Fortunately these are not common.

8. *Prevention and Treatment of Toxic Reactions.* Whereas there are no sure ways of preventing toxic reactions, small doses and constant vigilance permit the carrying out of gold therapy with a fair degree of safety. All allergic patients should be watched with particular care.[10] Mild albuminuria is a sign for caution, not for discontinuance of therapy,[16, 32] but with signs of active renal irritation (albumin of 2+ or more, red cells or casts in the urine, and increased blood urea nitrogen), gold should be discontinued permanently.[10] Eosinophilia may be a sign of poisoning,[55] and basophilic stippling of erythrocytes is a frequent finding.[43] There is no sure way to detect impending dermatitis; eosinophilia does not necessarily precede it or indicate it when present,[25] but pruritus often precedes it and is a warning signal. Increased menstrual flow may foreshadow a lowered platelet count and an impending purpura hemorrhagica.[49]

British Anti-Lewisite (BAL) (2, 3, Dimercaptopropanol) has proved to be an effective weapon for the control of some of the serious toxic reactions to gold,[12, 17, 49] as it has for other heavy metal poisonings. Ragan and Boots[47] used the drug in five patients with severe gold dermatitis and in four the pruritus and rash cleared up promptly; in one case, in which dermatitis was of long standing (three months' duration), the treatment was ineffective. Spectacular recovery with the use of BAL in one case of thrombopenic purpura and in one of agranulocytosis was reported.[37] Penicillin, acting as a temporary substitute for the phagocytic activity of granulocytes while granulopoiesis is being resumed, is an important adjuvant in the treatment of agranulocytosis.[7]

Fever Therapy. Artificial hyperpyrexia with temperature of 104° F. to 106° F. for several hours produced by the Kettering hypertherm or by electromagnetic induction, has been practically discarded.[6]. Such a procedure is exhausting, sometimes harmful, and relief is at the best temporary.

Roentgen Therapy. Roentgen therapy in peripheral rheumatoid arthritis has been disappointing to some observers[49] but in the experience of others it has frequently been successful in relieving local symptoms of pain and soreness,[33, 45, 62] especially when applied to one or two large joints that remain swollen and boggy. Because rheumatoid arthritis is a constitutional disease, roentgen therapy at best can be considered as a local measure and not as a complete form of therapy.[22] Kuhns and Morrison[35] treated 154 patients who had peripheral rheumatoid arthritis (without spondylitis). Improvement of the joints treated was pronounced in 22.7 per cent, moderate in 39.9 per cent, and slight in 16.8 per cent; no change was noted in the remaining 20.8 per cent. Improvement consisted of diminution of pain and swelling, local analgesia, and decrease in muscle spasm followed by increased range of active, painless motion.

Rest and Motion. The value of rest, both mental and physical, is universally recognized. But rest should not mean the total immobilization or "mummification" of the patient.[1] Complete bed rest is rarely indicated except during acute febrile stages, during severe exacerbation of joint manifestations, or during the initial phases of treatment. Overresting encourages muscle atrophy, contractures, and ankylosis;[44] some patients, overconscientious about rest and fearful of pain, may rest unduly and learn that "the price of too much comfort is crippledom."[41] When prolonged bed rest is needed, adequate posture should be maintained and bed exercises instituted.[36] The bed should be firm and nonsagging, pillows under the knees or shoulders should not be used, and indicated support with sandbags or foot board must be provided. Bed calisthenics, with breathing, muscle-setting, and trunk-stretching exercises, should be carried out several times daily, these being carefully timed to alternate with periods of rest. All joints, even though acutely inflamed, should be carried gently through the maximal range of motion once or more daily.[44]

Physical Therapy. Most observers consider physical therapy as a necessary adjunct to successful management. Home regimens consisting of simple physical measures often suffice.[30, 55, 64] Local heating of large joints can be carried out with a simple home-made luminous baker, clamp lamp, wet packs, or applications of paraffin wax if electricity is not available; contrast baths, paraffin dips or home whirlpool baths are useful for hands or feet; thermal tub baths each morning are helpful; massage can usually be provided if a member of the patient's family is instructed in a few simple strokes; active, passive, and resistive exercises can be carried out adequately at home.[30] By testing skin temperatures with various types of heat applications, Martin, Roth, Elkins and Krusen[38] found that the degree and duration of vasodilatation was the same whether the heat was moist or dry. General body heating (body baker, fever cabinet, Hubbard tank) resulted in more prolonged elevations of skin temperatures (feet and hands) than did local application of heat. In general, after the local application of heat to a part, the cutaneous temperature returns to basal

levels in about one-half to one-third less time than after the generalized application of heat.

Therapeutic exercise is best performed following massage and during the continued period of hyperemia.[30] Exercises have as their objects: (1) to preserve the function of the joint by preventing ankylosis; (2) to maintain the tone of muscles; (3) to prevent and overcome contractures and deformities.[9] They should be graduated from passive to active assistive and finally to active voluntary movements, depending on the degree of joint inflammation.

Prognosis. The literature has contained no report of a true control group receiving no treatment and followed for a period of sufficient duration to allow the natural course of rheumatoid arthritis to be appraised. However, Short and Bauer[57] studied a group of 250 patients treated only by general supportive measures for periods which averaged 9.6 years. The following results were reported: Improved, 53 per cent; stationary, 13 per cent; worse, 34 per cent. Fifteen per cent were in remission at the time of the last examination and 9.2 per cent could be considered as "five-year cures."

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