ble because many patients, from the standpoint of heredity, are incapable of meeting the exigencies of life and are therefore socially pathologic. In order to eliminate these disorders, the defects in education, government, religion, morality, philanthropy and even physical heredity have to be corrected. This ideal may be approached when there is a scientific understanding of the conditions necessary for normal social life. This ideal will never be attained by treating these patients for "colitis." It is only necessary to say in conclusion that the wisest measures should be directed toward the prevention of these disorders as well as toward the reclaiming of those who have already been caught in their meshes.

THE TREATMENT OF RHEUMATOID ARTHRITIS WITH LARGE DOSES OF VITAMIN D

A CRITICAL EVALUATION

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In 1935 Dreyer and Reed [1] reported that they had previously observed [2] marked clinical improvement in the rheumatoid arthritis of two patients during the time they were receiving massive doses of vitamin D for hay fever. This original report and other reports by the same authors [3] have resulted in an increasing interest in the value of vitamin D in the treatment of rheumatoid arthritis as shown by subsequent reports.[4]

Knowing that generalized decalcification is a common and at times an early manifestation of rheumatoid arthritis, one might be led to suspect that the chance observation of Dreyer and his co-workers [5] indicated that certain patients with rheumatoid arthritis suffer from some type of disease of calcium and phosphorus deficiency. If such were the case, then this chance observation might be of etiologic as well as of therapeutic significance. However, detailed studies of the calcium and phosphorus metabolism of patients with rheumatoid arthritis have failed to reveal metabolic changes of sufficient degree to allow one to conclude that the generalized decalcification is secondary to a primary disturbance of calcium and phosphorus metabolism.[6] This being true, one might conclude a priori that any improvement noted in patients following the administration of vitamin D was not the result of correcting a previously existing alteration of the calcium and phosphorus metabolism. An additional reason for doubting that such is not the modus operandi of massive doses of vitamin D is suggested by our failure to observe any material alteration in the course of the disease in patients receiving from 5,000 to 15,000 U. S. P. units of vitamin D daily for as long as from six to thirty months.[7] This dose of vitamin D, although not adequate for the cure of all diseases of calcium and phosphorus deficiency, is sufficiently large to correct a good percentage of them.[8]

Irrespective of the aforementioned facts, Dreyer and Reed [1] reported improvement in twenty-five of thirty-four patients with rheumatoid arthritis treated with large doses of vitamin D, and others [9] have reported equally encouraging results. Some reports [10] have been less enthusiastic. Other workers [11] have stated that further trial with this form of therapy is necessary before any final conclusions are drawn concerning its efficacy. The results obtained by previous workers are briefly summarized in table 1.

METHOD OF STUDY

Because of the therapeutic and etiologic significance that might be attached to the foregoing reports concerning a chronic disease of unknown etiology, it was deemed necessary to evaluate as critically as possible the therapeutic effectiveness of massive doses of vitamin D in the treatment of patients with rheumatoid arthritis. Since rheumatoid arthritis is a chronic disease of years' duration, characterized by remissions and relapses of varying length and degree, the course of the disease may vary considerably from patient to patient. Therefore, in a study of this type, designed to determine the therapeutic effectiveness of a particular form of therapy, one must of necessity require that each person serve as his own control. Only in this way can one determine whether or not the therapy has altered the course of the disease. If this precaution is not taken, one will all too frequently conclude that the observed improvement is the result of the therapy employed, whereas it may represent nothing more than a natural fluctuation in the course of the disease. This manner of controlled study can best be accomplished by choosing only those patients whose clinical course has been known for months or years on a constant regimen prior to the institution of any so-called specific form of therapy. Equally important in this type of study is an adequate follow-up period on the same

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From the Medical Clinic of the Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Massachusetts Department of Public Health.

1. Dreyer, Irving, and Reed, C. I.: The Treatment of Arthritis with Massive Doses of Vitamin D, Arch. Phys. Therapy **16**: 537 (Sept.) 1935.

2. Rappaport, B. Z., and Reed, C. I.: Viosterol of High Potency in Seasonal Hay Fever and Related Conditions, J. A. M. A. **101**: 105 (July 8) 1933.

3. Reed, C. I.: Irradiated Ergosterol—Clinical and Experimental Studies, Arch. Phys. Therapy **15**: 69 (Feb.) 1934. Rappaport, B. Z.; Reed, C. I.; Hathaway, M. L., and Struck, H. C.: The Treatment of Hay Fever and Asthma with Viosterol of High Potency, J. Allergy **5**: 541 (Sept.) 1934. Reed, C. I.: Symptoms of Viosterol Overdosage in Human Subjects, J. A. M. A. **102**: 1745 (May 26) 1934.

4. These include:
Livingston, S. K.: Vitamin D and Fever Therapy in Chronic Arthritis, Arch. Phys. Therapy **17**: 704 (Nov.) 1936.
Vrtiak, E. G., and Lang, R. S.: Observations on the Treatment of Chronic Arthritis with Vitamin D, J. A. M. A. **106**: 1162 (April 4) 1936.
Holbrook, W. P., and Hill, D. F.: Treatment of Atrophic Arthritis, J. A. M. A. **107**: 34 (July 4) 1936.
Wyatt, B. L.; Hicks, R. A., and Thompson, H. E.: Massive Doses of Vitamin D in the Treatment of Proliferative Arthritis, Ann. Int. Med. **10**: 534 (Oct.) 1936.
Farley, R. T.: Management of Arthritis, Illinois M. J. **71**: 74 (Jan.) 1937.
Steck, I. E.: Clinical Experience in the Treatment of Arthritis with Massive Doses of Vitamin D, ibid. **71**: 243 (March) 1937.
Steck, I. E.; Deutsch, H.; Reed, C. I., and Struck, H. C.: Further Studies on Intoxication with Vitamin D, Ann. Int. Med. **10**: 951 (Jan.) 1937.
Hench, P. S.; Bauer, Walter; Ghrist, David; Hall, Francis; Holbrook, W. P.; Key, J. A., and Slocumb, C. H.: The Present Status of Rheumatism and Arthritis: Review of American and English Literature for 1936, Ann. Int. Med. **11**: 1089 (Jan.) 1938.

5. Dreyer and Reed.[1] Rappaport and Reed.[2] Reed.[3] Rappaport, Reed, Hathaway and Struck.[3]

6. Bauer, Walter, and Ropes, M.: Unpublished data.

7. Bauer, Walter, and Short, C. L.: Unpublished data.

8. Bauer, Walter: The Parathyroid Glands in Health and Disease, Virginia M. Monthly **62**: 123 (June) 1935. Miles, L. M., and Feng, C. T.: Calcium and Phosphorus Metabolism in Osteomalacia, J. Exper. Med. **41**: 137 (Jan.) 1925.

9. Livingston.[4] Farley.[4] Steck.[4]

10. Vrtiak and Lang.[4] Holbrook and Hill.[4] Wyatt, Hicks and Thompson.[4]

11. Holbrook and Hill.[4] Hench, Bauer, Ghrist, Hall, Holbrook, Key and Slocumb.[4]

constant regimen employed prior to the institution of the form of therapy being studied. If each patient studied is so controlled, then one is best able to conclude whether the observed improvement or alteration in the course of the disease during and after treatment represents a therapeutic effect, a chance remission or the natural course of the disease. In all fairness to the form of therapy being studied, one should choose patients whose disease process is reversible. Any therapeutic measure employed in the treatment of rheumatoid arthritis should effect clinical improvement with great regularity in most patients before one has the right to suspect that one is dealing with a specific therapeutic agent. In studies of this type it is equally important to record improvement as accurately as possible by every available method. This is best accomplished by recording separately subjective, objective and laboratory evidence of improvement as well as grading the final result on the basis of all three. This method of appraisal enables one to evaluate more accurately any psychic effect, such as is so frequently encountered in patients with chronic disease following the institution of any new form of therapy.

Failure to consider these many facts in times past has been responsible for many premature therapeutic and etiologic claims, the inspiring of false hope in patients at great financial expense and at times progression of the disease because a good general regimen was not adhered to during the time the new form of therapy was being employed. It is extremely difficult to draw conclusions from much of the data presented in the reports concerning the therapeutic effectiveness of large doses of vitamin D in rheumatoid arthritis because the patients were not rigidly controlled and the degree of improvement was not accurately recorded.

We have observed eighteen patients with typical rheumatoid arthritis prior to, during and after the administration of large doses of vitamin D. Only five (66, 90, 286, 328 and J. H.) of the eighteen patients were hospitalized during the period of treatment. From table 2 one notes that in all instances the arthritis was in a stationary or progressive state prior to the institution of vitamin D therapy. It will be further noted that the duration of the arthritis, its severity and the extent of involvement varied from patient to patient. The observed therapeutic effects are recorded separately as subjective improvement, objective improvement, fluctuation in weight and alteration in the corrected sedimentation rate [12] as well as the total end result. Determinations of fasting serum calcium,[13] serum phosphorus [14] and serum phosphatase [15] were made every

TABLE 1.—*Results Observed by Other Authors Following the Administration of Massive Doses of Vitamin D to Patients with Rheumatoid Arthritis*

Authors	Number of Patients	Daily Dose (U. S. P. Units)	Duration of Therapy	Other Measures Used	Per Cent Improved	Authors' Comments
Dreyer and Reed [1]	34*	200,000-500,000 occasionally up to 1,000,000	Not stated	Not stated	73†	Improvement evidenced locally by diminution of swelling and pain in the joints as well as by increased motion of the joints; general improvement consisted of improved nutritive state; greater muscular strength, less fatigability, improved gastrointestinal function and decreased vasomotor instability; "toxic symptoms often present without hypercalcemia"; "hypercalcemia often without associated toxicity"
Livingston [4]	14	200,000-600,000	"Continued over an indefinite period of time"	Fever therapy in 9 cases	86‡	Improvement noted similar to that reported by Dreyer and Reed [1]; sedimentation rates reduced; "toxicity not associated with hypercalcemia"; "fever therapy in conjunction with vitamin D caused more rapid clinical improvement than vitamin D alone"
Farley [4]	27§	200,000-600,000 in one case 1,000,000	Not stated	"Fever therapy in some"	100	Some patients treated for first time; others had received treatment elsewhere for as long as 5 to 6 years without benefit; decrease in pain, increased motion of the joints and improved nutritional state were observed; sedimentation rates lowered; roentgenograms showed recalcification of bone and reconstruction of cartilage
Vrtiak and Lang [4]	20	150,000-200,000	Averages: In markedly improved group—3 months; moderately improved—10 months; slightly improved—7¾ months; unimproved—3½ months	Not stated	60 (2 cases marked, 6 moderate, 4 slight)	Roentgenograms taken following completion of therapy failed to reveal increased bone density (5 cases); concluded that results are similar to those obtained with other forms of therapy; therefore believe conservative attitude should be maintained before vitamin D is accepted as a specific form of therapy
Wyatt, Hicks and Thompson [4]	40	200,000-300,000	Not stated	General measures	20	Patients under observation for at least 6 months prior to treatment; improvement determined by bettered general physical status, decreased signs and symptoms of the joints; sedimentation rates, morphologic blood pictures, agglutination reactions for streptococci and serum calcium and phosphorus values were followed
Steck [4]	?#	Usually 150,000-300,000 (some higher)	6 months' trial (with rest periods); continued beyond if improved	General measures	"75-80% can be benefited"	Noted improvement similar to that described by Dreyer and Reed [1]; also, decreased sedimentation rates and increased red blood cell counts; roentgenograms showed recalcification of bones
Holbrook and Hill [4]	25	200,000-300,000	4 months	General measures	?	Noted less pain in 5 patients and marked reduction in sedimentation rates in 4; authors state that sufficient time has not elapsed to evaluate therapy
Hench et al.[4]	"About 25"	250,000-600,000	1-2 years	Not stated	?	"Reduction in pain and soreness, and increase in well being in some patients; little change in articular lesions"

* Three other cases were listed as "mixed." These included one "infectious and gonorrheal" and two "menopausal and rheumatoid." Two of these three patients improved.
† Results in three cases listed as "still uncertain."
‡ Improvement in four of the five patients treated with vitamin D alone, whereas eight of the patients treated with fever therapy in addition improved.
§ Author included all types of arthritis.
# Number of patients treated not stated.

12. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, J. Clin. Investigation **8**: 545 (June) 1930.
13. Fiske, C. H.: Method for Calcium Determination, Unpublished data.
14. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**: 375 (Dec.) 1925.
15. Bodansky, Aaron: Phosphatase Studies. II. Determination of Serum Phosphatase. Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**: 93 (June) 1933.

TABLE 2.—*Description of Patients with Rheumatoid Arthritis and*

Case;* Sex; Age, Years	Characterization of Arthritis: Duration of Disease	Extent of Involvement	Activity of Disease	Total Severity	Time Observed Before Therapy	Course During Pretreatment Period	Daily Dose of Vitamin D (U. S. P. Units)†	Duration of Therapy	Sedimentation Rates, Mm. per Min.: Just Prior to Therapy	During Therapy	Following Therapy
32 ♀, 28	5 yrs.	Moderate	Moderate	Moderate	4½ yrs.	Slowly progressive	80,000 to 200,000‡	13 mos.	Low 0.68 High 1.11 Last 0.82	Low 0.45 High 0.86 Last 0.45	Not done
40 ♀, 61	7 yrs.	Extensive	Moderate	Moderate	4 yrs.	Stationary except for mild partial remission	60,000 to 160,000	7 wks.	Low 1.08 High 1.42 Last 1.19	Low 0.56 High 1.28 Last 1.14	1.13-1.15 (4 mos.)
41 ♀, 64	8 yrs.	Mild	Mild	Mild	4 yrs.	Very slowly progressive	(*a*) 20 000 to 160,000	5 mos.	Low 0.73 High 0.98 Last 0.65	Low 0.69 High 1.11 Last 0.68	0.69 (2 mos.)
							(*b*) 160,000 to 220,000	5 wks.	No rates done		
66 ♀, 17	9 yrs.	Mild	Moderate	Moderate	2 yrs.	Stationary	20,000 to 80,000	3 mos.	Low 1.64 High 1.97 Last 1.62	Low 1.48 High 1.56 Last 1.56	1.68 (9 mos.)
90 ♀, 49	7 yrs.	Moderate	Moderate	Moderate	2 yrs.	Slowly progressive	20,000 to 160,000	4 mos.	Low 1.67 High 1.94 Last 1.94	Low 1.24 High 1.70 Last 1.70	1.62-1.86 (15 mos.)
120 ♂, 51	4 yrs.	Extensive	Marked	Severe	2 yrs.	Occasional periods of slight improvement; on the whole, stationary	20,000 to 160,000	10 mos.	Low 1.02 High 1.69 Last 1.59	Low 1.21 High 1.65 Last 1.21	1.38-1.52 (5 mos.)
127 ♂, 26	10 yrs.	Extensive	Moderate	Moderate	4 yrs.	Slight progression of disease	80,000 to 160,000	15 wks.	Low 0.75 High 1.31 Last 1.25	Low 1.12 High 1.19 Last 1.12	1.04 (7 mos.)
181§ ♀, 29	7 yrs.	Mild	Mild	Mild	5 yrs.	Many good and bad periods; on the whole, stationary	80,000 to 160,000	11 mos.	Low 1.50 High 1.91 Last 1.52	Low 1.20 High 1.95 Last 1.95	1.63-1.43 (4 mos.)
194 ♂, 51	3 yrs.	Extensive	Moderate	Moderate	1½ yrs.	Practically stationary; at times, slight improvement	80,000 to 160,000	8½ mos.	Low 1.78 High 2.03 Last 1.96	Low 0.96 High 1.99 Last 1.99	1.45-1.98 (7 mos.)
221# ♂, 60	25 yrs.	Mild	Marked	Severe	3 yrs.	Slowly progressive	80,000 to 160,000¶	8 mos.¶	Low 1.25 High 1.68 Last 1.35	Low 1.11 High 1.64 Last 1.63	1.48-1.32 (6 mos.)
229§ ♀, 49	7 yrs.	Mild	Moderate	Moderate	4 yrs.	Slowly progressive	80,000 to 160,000	6 mos.	Low 0.68 High 1.12 Last 1.12	Low 0.53 High 0.84 Last 0.53	0.70 (7 mos.)
286 ♀, 21	5 yrs.	Moderate	Moderate	Moderate	6 mos.	Slowly progressive	(*a*) 40,000 to 200,000	3⅓ mos.	Low 1.42 High 1.69 Last 1.32	Low 0.83 High 1.03 Last 1.03	1.04-1.48 (5 mos.)
286	Because of relapse, treatment resumed 12 months later						(*b*) 120,000 to 300,000‡	4 mos.	Low 0.94 High 1.51 Last 1.22	Low 0.62 High 1.22 Last 0.63	0.84 (2+ mos.)
328 ♂, 42	6 yrs.	Extensive	Marked	Moderate	3 mos.	Stationary	80,000 to 160,000	1 yr.	Low 0.63 High 1.61 Last 0.63	Low 0.75 High 1.89 Last 1.00	Not done
335 ♀, 50	1 yr.	Extensive	Marked	Severe	2 mos.	Stationary	45,000 to 60,000	6 mos.	Low 1.15 High 1.45 Last 1.26	Low 0.78 High 1.63 Last 1.24	1.09-0.92 (2 mos.)
J. H. ♀, 11	2 yrs.	Moderate	Moderate	Moderate	6 mos.	Slowly progressive	48,000 to 60,000	3 mos.	Low 0.53 High 0.70 Last 0.56	Low 0.53 High 0 82 Last 0.67	0.48-0.79 (1½ mos.)
A. A. B.‖ ♂, 51	8 mos.	Extensive	Marked	Severe	6 mos.	Rapidly progressive	140,000 to 160,000	3 mos.	Low 1.59 High 1.78 Last 1.78	Low 1.58 High 1.72 Last 1.60	1.60-1.81 (5 mos.)
F. D.‖ ♀, 38	5 mos.	Mild	Mild	Mild	1 mo.	Slowly progressive	60,000 to 80,000	13 mos.	Low 0.63 High 0.81 Last 0.77	Low 0.59 High 0.72 Last 0.59	0.61-0.85 (3 mos.)
C. M.‖ ♀, 60	5 mos.	Moderate	Moderate	Moderate	5 mos.	Slowly progressive	250,000‡	6 mos.	Low 1.07 High 0.74 Last 1.08	Low 0.84 High 1.04 Last 1.15	1.17-0.98 (6 mos.)

* The numbers listed here refer to the patients with rheumatoid arthritis who have been studied in detail and have been reported on in the past. These patients will be referred to by the same number in the detailed publications concerning rheumatoid arthritis which will appear later.

§ These cases have been reported by the same number in the paper entitled "The Treatment of Rheumatoid Arthritis with Colloidal Sulfur."

This patient experienced complete remission for eighteen years. Present attack of seven years' duration.

Results Observed Following Treatment with Large Doses of Vitamin D

Toxic Manifestations		Observed Effects			
Symptoms	Hypercalcemia, Mg. per 100 Cc.	Subjective Changes	Objective Changes	Weight Changes	End Results and Comments
Nausea, epigastric discomfort	11.1 on 2 occasions	Joint symptoms not affected; fewer constitutional symptoms; stronger	None	Gained 14 pounds	Gained weight, some subjective general improvement; decreased sedimentation rate; no objective change
Nausea, vomiting, anorexia, diarrhea, headache	12.5 on 1 occasion—12 days after first appearance of toxic symptoms, 8 days after discontinuing vitamin D	None	None	Lost 4 pounds	No changes observed; sedimentation rate of 0.56 obtained at time of hypercalcemia; final sedimentation rate unaltered
None	12.0 on 1 occasion	None	None	Unchanged	No change in weight, sedimentation rate, or clinical condition
None	Not encountered	Less pain; slight general improvement	No change; one new joint (temporomandibular) became involved during therapy	Unchanged	Subjective improvement; one joint became involved for the first time during period of treatment; no change in weight or sedimentation rate
Nausea, vomiting, anorexia, epigastric pain	11.0 to 16.0, 12 weeks' duration	Less pain; slight general improvement	Slight reduction in joint swelling; slight increase in joint motion	Unchanged	Slight subjective and objective improvement; sedimentation rate not significantly altered; no weight change
"Indigestion"	11.8 on 1 occasion; became normal without altering dosage	Much stronger, less fatigue, less pain	More alert in appearance and activity; joint showed freer motion	Gained 6 pounds	Moderate subjective improvement; slight improvement objectively, mainly in general nutritive state; motions of joints freer, but soft tissue swelling and mobility unaltered; slight weight gain; sedimentation rate lowered
None	11.2 to 11.4, 3 weeks' duration	None	None	Unchanged	Far advanced case with joint deformities; some joints of recent involvement; no change of any kind noted while under treatment; patient himself discontinued treatment because of disappointing results
Nausea, epigastric distress, anorexia, diarrhea	11.6 and 12.8 on 2 isolated occasions; 11.4 to 12.9, 3 months' duration; 12.0 to 11.1, 2 months' duration	None	None	Unchanged	Had exacerbation and remission while taking vitamin D; condition unchanged; sedimentation rate rose
Nausea, vomiting, heart burn, anorexia	12.8 to 12.9, 4 weeks; still 11.0, 15 days later 12.0, 1 additional occasion	Slight improvement in general strength; less joint pain	Slight reduction of joint swelling	Unchanged	Slight subjective and objective improvement; no change in weight or sedimentation rate; lowered sedimentation rate during therapy observed at time of hypercalcemia
Nausea, anorexia, frequency of urination, drowsiness	12.2 and 16.6 on 2 occasions	Improved at beginning (general strength, less pain); relapsed during course of treatment	None	Unchanged	Subjective improvement with onset of therapy, followed by relapse; no other type of improvement noted
Headache	11.7 on 1 occasion, dropped to normal without altering dosage	Improved at beginning; later relapsed	None	Unchanged	Large psychic element; subjectively improved at first, later discontinued therapy because of relapse; sedimentation rate decreased despite failure to improve
None	Not encountered	Marked improvement—less pain and stiffness; felt stronger and noted less fatigue	Marked improvement; reduction of swelling, disappearance of effusions, better joint motion	Gained 21 pounds	Marked improvement subjectively and objectively, with fall in sedimentation rate; gained 21 pounds; improvement lasted only a few weeks after therapy was discontinued
Nausea, epigastric discomfort, anorexia	11.9 and 12.0 on 2 occasions	Same improvement as experienced during first course but less marked and slower	Same as first course, but not so marked	Unchanged	During second period of therapy, subjective and objective improvement and drop in sedimentation rate noted; no weight change; improvement very slow
None	11.1 to 12.6, 4 weeks	Felt stronger and less pain at first; later relapsed to original state	None	Gained 10 pounds	Gained weight but showed no subjective or objective change at end of therapeutic trial; sedimentation rate higher at end
Nausea, epigastric distress	14.2 to 11.5, 12 weeks; 11.2 to 12.4, 13 weeks	Slight improvement in general strength	None	Unchanged	Except for slight subjective improvement, patient showed no change in condition; weight and sedimentation rate not altered
Anorexia	11.9 to 11.3, 2 weeks	None	None	Unchanged	Typical adult type of rheumatoid arthritis in a child; no change in clinical condition, weight or sedimentation rate while receiving therapy
None	11.2 to 11.9, 4 weeks	None	None	Unchanged	No change of any kind observed
Toxic symptoms persisted until the dose was reduced to 60,000 units	11.3 on 1 occasion	Moderate remissions and relapses while on a constant dose	Joint signs fluctuated markedly during treatment	Unchanged	Had moderate remissions and relapses while under treatment; final condition unchanged either subjectively or objectively; sedimentation rate fluctuated during course but final reading lower than pretreatment figure; no weight change
Marked anorexia, nausea and vomiting	11.6 to 12.5, 4 months	Slight subjective improvement	Swelling of wrists and fingers varied greatly during treatment	Lost 8 pounds	Slight subjective and objective improvement; general physical status and sedimentation rate unchanged

‖ Private patient of one of the authors (W. B.).
‡ Doses of 200,000 U. S. P. units and over were reached only with a preparation of vitamin D in sesame oil.
¶ Includes period of four months when drug was taken irregularly at the rate of about 30,000 to 80,000 U.S.P. units daily.
† In this column *a* indicates first course of treatment and *b* second course of treatment.

four to eight weeks in order to establish how often hypercalcemia resulted and whether or not suspected toxic symptoms occurred at the same time. Vitamin D[16] in the form of Drisdol (1 drop = 250 U. S. P. units) was administered for a short time to the first five patients in the series. These and the remaining patients subsequently received a more concentrated preparation, crystalline vitamin D in propylene glycol (1 drop = 1,000 U. S. P. units) or in sesame oil (1 drop = 25,000 U. S. P. units). One third or one fourth of the total daily dose was administered with each meal, and the fourth (when given) was taken at bedtime. All preparations were administered in milk, because Lewis[17] has shown that the antirachitic vitamin dissolved in propylene glycol is better utilized in the medium of milk than in the medium of corn oil. Throughout the period of study all patients were kept on a constant therapeutic regimen consisting of a high vitamin, high caloric diet (unless overweight), regular rest periods, daily physical therapeutic measures, vitamin B in the form of yeast and a constant ration of acetylsalicylic acid. No new therapy was added during the period of observation.

RESULTS

Subjective Improvement.—As can be seen from tables 2 and 3, if one were to judge solely on the basis of subjective improvement one might conclude that a good percentage of the patients with rheumatoid arthritis were benefited by vitamin D therapy. Subjective improvement, consisting of increased strength and feeling of well being, less of the myasthenia gravis-like fatigability and a reduction of pain and stiffness was reported by twelve of the eighteen patients. In four instances such improvement was short lived, being experienced only during the first few weeks of therapy. In the other eight cases such improvement was present throughout the period of treatment. In one instance it was marked, in another moderate, and in six slight. Such improvement was not maintained more than a few weeks following the discontinuance of vitamin D therapy.

Objective Improvement.—When evidence of improvement is judged on the basis of objective changes, one notes from tables 2 and 4 that only five of the eighteen patients experienced benefit from vitamin D therapy. These five patients had also experienced subjective improvement. In four the objective improvement was slight; in one it was marked. From table 2 it will be seen that the patient (286) in whom improvement was marked received large doses of vitamin D on two different occasions and each time experienced marked objective as well as subjective improvement. The improvement observed each time consisted of marked reduction of soft tissue swelling, disappearance or marked reduction of effusions of the knee joints and an increase in motion of the joints. In the other three cases the improvement was less marked and consisted of slight reduction of the soft tissue swelling and increase in motion of the joints. In one case (66) involvement of the new joints occurred during therapy. Two patients (F. D. and C. M.) experienced marked remissions and exacerbations of signs and symptoms in the joints during the period of treatment, yet the dosage of vitamin D was kept constant throughout this time.

Weight Gain.—Improvement as measured by an appreciable weight gain (5 or more pounds) was observed in five patients (32, 120, 286, 328 and F. D.). Two of these patients (120 and 286) had noted subjective and objective improvement. Such beneficial effects were most marked in patient 286, who gained a total of 21 pounds (9.5 Kg.). Patients 32 and 328 had noted only subjective improvement, whereas Mrs. F. D. had exacerbations and remissions of both subjective and objective change.

Effect on the Sedimentation Rate.—From experience to date, the corrected erythrocyte sedimentation rate[12] has proved to be the most reliable laboratory test for determining the activity of rheumatoid arthritis.[18] This one objective laboratory test was performed at regular intervals before, during and after vitamin D therapy in order to determine whether the encountered variations in the sedimentation rate paralleled the observed clinical course of the disease.

In order to be consistent in judging when a decrease in the corrected sedimentation rate was significant, it was found necessary to follow some arbitrary rule.

TABLE 3.—*Subjective Improvement*

Marked improvement during entire period of therapy	1
Moderate improvement during entire period of therapy	1
Slight improvement during entire period of therapy	6
Improved only at beginning of therapy	4
No improvement at any time	6

TABLE 4.—*Objective Improvement*

Marked improvement	1
Slight improvement	4
No improvement	13

The one described here was finally adopted. In cases in which the sedimentation rate had varied between 0.5 and 1 mm. per minute a decreased rate was not considered significant unless it had fallen 0.15 mm. or more below the previously recorded rate. When the sedimentation rate had varied between 1 and 1.5 mm. per minute, a decrease of 0.2 mm. or more was considered significant. In cases in which the rate had been 1.5 mm. or more per minute a reduction was not considered significant unless it exceeded 0.3 mm. per minute.

In order to conserve space and yet give the reader some idea as to the changes observed in the curves of the sedimentation rate of each patient during the pretreatment, treatment and follow-up periods, the maximal-minimal variations for each patient are presented in table 2. Detailed curves of the sedimentation rate of four patients are presented in the accompanying chart. From the chart and table 2 one notes that alterations in the curves of the sedimentation rate were observed in only seven of the eighteen patients, but in only five was it significant. In cases 120 and 286 (as seen in the chart and in table 2) subjective and objective improvement took place at the same time. In case 286 a reduction in the sedimentation rate and clinical improvement were noted each time vitamin D was administered. In

16. The Winthrop Chemical Company placed the vitamin D preparations at our disposal for this study.

17. Lewis, J. M.: Clinical Experience with Crystalline Vitamin D: The Influence of the Menstruum on the Effectiveness of the Antirachitic Factor, J. Pediat. **6**: 362 (March) 1935.

18. Short, C. L.; Dienes, Louis, and Bauer, Walter: Rheumatoid Arthritis: A Comparative Evaluation of the Commonly Employed Diagnostic Tests, J. A. M. A. **108**: 2087 (June 19) 1937.

two other patients only subjective improvement was noted. The fifth patient, showing a lowered sedimentation rate, experienced no clinical improvement. Eleven of the remaining thirteen patients showed no significant alteration in the curve of the sedimentation rate. The sedimentation rates of the other two patients were increased, although both patients had considered themselves subjectively improved during the first weeks of therapy.

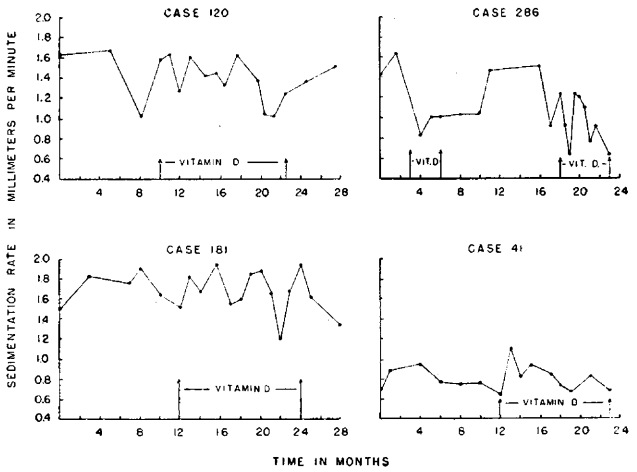
The observed changes in the sedimentation rates are difficult to interpret. That they cannot be of great significance is attested by the fact that both subjective and objective improvement was observed in only two of the eighteen cases studied. In fourteen cases the degree of variation encountered was as great in the pretreatment and follow-up periods as it was in the therapy period. In the chart, the variations in the curves of the sedimentation rates of the two patients who improved subjectively and objectively are compared with those of two patients who did not. These illustrated curves of the sedimentation rate serve to stress the fact that judging clinical improvement is extremely difficult even when a purely objective laboratory test is employed as the measuring stick. For instance, in case 120 the lowest sedimentation rate observed in the period of therapy was no lower than had been observed in the pretreatment period. One further observes that the sedimentation rate had begun to rise before vitamin D was discontinued. Although the changes observed in cases 120 and 286 may very well have been the result of vitamin D therapy, there is no denying the fact that they may represent, at least in part, the natural fluctuations that one frequently observes in patients receiving no specific therapy. Certainly one is not justified in drawing conclusions concerning improvement based on the sedimentation rate unless a significant sustained lowering takes place with some regularity in most patients during the period of therapy. Not having observed such an effect with any regularity in the eighteen cases studied, one is forced to conclude that vitamin D does not have any beneficial effect on the clinical course of rheumatoid arthritis as judged by the curve of the sedimentation rate. It was interesting to note that the greatest reductions in sedimentation rates frequently occurred at the time of the hypercalcemia. Such drops in the sedimentation rate were usually transient even though the hypercalcemia persisted. Variations of this type were encountered as often in those patients who did not experience clinical improvement as in those who did. This type of change in the sedimentation rate is probably directly related to the hypercalcemia and serves as further evidence that the variations in the sedimentation rates of erythrocytes cannot be ascribed to any one factor.[19]

Final Result and Duration of Improvement.—The improvement noted always took place slowly. The best clinical and laboratory results were observed in case 286. These were observed each time vitamin D was administered but were never sudden or dramatic. The patient was hospitalized throughout each course of vitamin D therapy. The beneficial results in this case as in the others were short lived. During the follow-up study it was noted that the arthritis gradually became as severe as it had been in the pretreatment period. Such changes were obvious in a few weeks. The other three patients who had experienced subjective and objective improvement fared no better. In the fourteen cases not materially influenced by vitamin D the arthritis ran the same pretreatment course during and after the period of administration of vitamin D. Results such as these serve to emphasize the fact that follow-up studies are needed.

19. Ropes, Marion W.; Rossmeisl, Elsie, and Bauer, Walter: The Relationship Between the Erythrocyte Sedimentation Rate and the Plasma Proteins, J. Clin. Investigation **17**: 520 (July) 1938.

HYPERCALCEMIA AND VITAMIN D TOXICITY

The pretreatment calcium, phosphorus and phosphatase values of all eighteen patients were normal, indicating as have previous studies that the calcium and phosphorus metabolism of rheumatoid arthritic patients as judged by the blood examination is normal. In sixteen of the eighteen patients hypercalcemia developed at some time during the period of vitamin D therapy. From table 2 it will be noted that hypercalcemia was noted only on one or two occasions in nine of the eighteen patients. In five instances (32, 41, 120, 127 and 229) there were no significant associated symptoms of toxicity, and the serum calcium returned to normal without alteration of the dose of vitamin D.



These curves of sedimentation rates illustrate how difficult it is to interpret clinical improvement even though it is based on an objective laboratory test. Patients 120 and 286 experienced both subjective and objective improvement while receiving large doses of vitamin D, whereas patients 181 and 41 did not.

In cases 40, 221, 286 and F. D. either vitamin D was discontinued or the dose was reduced because of the degree of hypercalcemia or the severity of the toxic symptoms. In the other seven cases fasting serum calcium values varying from 11.2 to 16 mg. per hundred cubic centimeters persisted for weeks (from three to twenty-five) unless the dose of vitamin D was reduced or the drug discontinued. In most instances such values for hypercalcemia were not encountered until the dose was maintained between 160,000 and 200,000 U. S. P. units daily. However, a hypercalcemia of from 11.2 to 14.2 mg. per hundred cubic centimeters was observed in patient 335 for a period of twenty-five weeks, during which time the daily dose of vitamin D never exceeded 60,000 U. S. P. units. We were unable to exceed a dose of 200,000 U. S. P. units daily of the crystalline vitamin D in propylene glycol administered in milk without encountering toxic symptoms. Although the patients did tolerate larger doses of the crystalline vitamin D-sesame oil preparation, in no instance could we exceed a dose of 300,000 U. S. P. units daily without encountering serious toxic symptoms or hypercalcemia.

The toxic symptoms observed were similar to those previously described,[20] consisting of anorexia, nausea, vomiting, epigastric distress or pain, diarrhea, headache, drowsiness, polyuria, polydipsia and nocturia. In some instances these symptoms were sufficiently marked to be alarming. Both the toxic symptoms and hypercalcemia often persisted for several weeks following discontinuance of the vitamin D therapy. An increased fasting serum phosphorus was observed on only two occasions. In these two instances values of 5.1 and 5.5 mg. per hundred cubic centimeters were observed with serum calcium values of 11.3 and 16.6 mg. In only one case did the serum phosphatase rise above a value of 5 Bodansky units. In this single instance a value of 6.5 units was observed with a normal serum calcium and phosphorus (10.2 and 3.4 mg. per hundred cubic centimeters respectively). As can be seen from table 2, the degree of hypercalcemia, its duration and the severity of the associated toxic symptoms were in no way related to the observed subjective and objective changes.

COMMENT

From the results observed in this series of patients with rheumatoid arthritis treated with large doses of vitamin D it is impossible to conclude that such therapy materially influences the course of the disease. Certainly the results are too disappointing to allow one to entertain the thought that one might be dealing with a specific therapeutic agent. If one were to judge solely on the basis of subjective and objective improvement experienced during the period of therapy only, one might be more enthusiastic concerning the value of vitamin D as a therapeutic agent for rheumatoid arthritis. When, however, a group of rheumatoid arthritic patients observed on the same constant general therapeutic regimen before, during and after the administration of large doses of vitamin D fail to show both clinical and laboratory evidence of improvement and no material alteration in the course of the disease, one is forced to conclude that the results are disappointing. Such an experience serves to stress the fact that each patient should serve as his own control and that adequate follow-up periods are necessary to judge the therapeutic results when one is dealing with a chronic disease such as rheumatoid arthritis. One might contend that beneficial effects are observed only while vitamin D is being administered. The data herein presented nullify such a contention. It might be argued that large doses of vitamin D are a useful addition to the therapeutic armamentarium employed in treating this disease. From our results we would conclude that the same general beneficial effects are experienced as often when vitamin D is administered in the usual therapeutic doses and that such dosages do not entail the risks attendant on hypercalcemia.

One might argue that failure to administer the same large doses of vitamin D employed by others is adequate reason for our not having obtained the same beneficial results previously reported. Evidence in favor of such an argument is readily obtained from tables 1 and 2, which show that only three patients in our series ever received a dose exceeding 200,000 U. S. P. units daily, whereas other workers have administered as much as 500,000 U. S. P. units or more daily. Because severe toxic symptoms or hypercalcemia were encountered in all but three patients whenever the daily dose exceeded 200,000 U. S. P. units, we did not feel justified in employing larger doses. As can be seen from table 2, hypercalcemia was encountered more frequently than were toxic symptoms. Of these two complications of vitamin D therapy the hypercalcemia is the more serious, because if it is allowed to persist extensive calcium deposits and other pathologic changes may ensue.[21]

Other workers[22] have reported that hypercalcemia and toxic symptoms are rarely encountered when large doses of vitamin D are administered, yet in our small series of patients receiving smaller doses hypercalcemia was observed in sixteen of the eighteen patients, and in seven cases it persisted for weeks unless the dose of vitamin D was reduced or the drug was discontinued. There appears to be only one possible explanation for such discrepancies, namely that the vitamin D preparation administered to the patients in this series was always given in milk. The medium of milk, according to the work of Lewis,[17] allows for better utilization of a solution of crystalline vitamin D in propylene glycol than does the medium of corn oil (the medium employed by Reed and others). Lewis's results indicate that the antirachitic potency of such crystalline vitamin D preparations is increased tenfold when administered in milk. Whether a similar increased vitamin D potency resulted in our studies in consequence of the administration of the vitamin in milk we are unable to say with certainty. The high percentage of patients in whom hypercalcemia and toxic symptoms developed would suggest that such an increase in potency had occurred. If it did, then we were administering larger doses than the dosage in table 2 indicates. If this is true, the argument that failure to obtain better clinical results in this series was due to the employment of smaller doses no longer holds.

In order to be certain that the medium of propylene glycol might not be responsible for the high percentage of patients exhibiting toxic symptoms, this possibility was investigated. Propylene glycol was administered in milk to five patients in doses the same as or larger than they had received when taking the propylene glycol containing vitamin D. In no instance were any symptoms experienced; therefore this possibility is untenable.

Some workers[23] have contended that the simultaneous administration of yeast will aid greatly in controlling or preventing the toxic symptoms associated with large doses of vitamin D. Such was not our experience. As previously stated, all our patients received yeast throughout the period of observation, yet in a large percentage toxic symptoms developed.

No increased calcification or intra-articular changes were demonstrable roentgenographically in this series or others[24] following the administration of vitamin D. This is not surprising. We know that we are not dealing with a calcium and phosphorus deficiency disease and that the ability of articular cartilage to repair itself is at best very limited.[25] Therefore we are skeptical of statements[26] to the effect that filling in of

20. Rappaport, Reed, Hathaway and Struck.[3] Vrtiak and Lang.[4] Steck, Deutsch, Reed and Struck.[4] Hench, Bauer, Ghrist, Hall, Holbrook, Key and Slocumb.[4]

21. Rappaport, Reed, Hathaway and Struck.[3] Steck, Deutsch, Reed and Struck.[4]

22. Dreyer and Reed.[1] Livingston.[4] Vrtiak and Lang.[4]

23. Reed.[3] Livingston.[4]

24. Vrtiak and Lang.[4]

25. Bennett, G. A., and Bauer, Walter: A Study of the Repair of Articular Cartilage and the Reaction of Normal Joints of Adult Dogs to Surgically Created Defects of Articular Cartilage, "Joint Mice" and Patellar Displacement, Am. J. Path. **8**: 499 (Sept.) 1932. Bennett, G. A., and Bauer, Walter: Further Studies Concerning the Repair of Articular Cartilage in Dog Joints, J. Bone & Joint Surg. **17**: 141 (Jan.) 1935.

26. Farley.[4] Steck.[4]

rarefied areas and reconstruction of articular cartilage in cases of rheumatoid arthritis have been observed in consequence of large doses of vitamin D.

Most therapeutic discoveries are soon acclaimed by others and the original reports of the discoverers substantiated by further and more detailed reports. As in the case of many other previously discovered antirheumatic remedies, such acclaim and substantiations have not appeared. Until they do, one is hardly justified in prescribing an expensive therapeutic agent capable of producing toxic symptoms and serious pathologic changes. For these reasons the Council on Pharmacy and Chemistry of the American Medical Association has been unwilling to include in New and Nonofficial Remedies Ertron and other high potency viosterol preparations as being specific in the treatment of arthritis.[27] If the beneficial results from vitamin D are to be ascribed to some impurity contained in the preparations employed, it had best be isolated and tested separately.

SUMMARY AND CONCLUSIONS

1. The effect of massive doses of vitamin D has been observed on eighteen patients with rheumatoid arthritis.

2. Observations prior to treatment showed that all the patients were in a stationary or slowly progressive state.

3. Subjective improvement lasting throughout the period of therapy was observed in eight cases. In only three instances was this accompanied by objective improvement and in only one was it marked. Such improvement was short lived when therapy was discontinued.

4. Only five patients showed a significant alteration in the curves of their sedimentation rate, and only two of these were improved subjectively and objectively.

5. Five patients gained weight during treatment.

6. Our results indicate that the administration of massive doses of vitamin D in rheumatoid arthritis is of little or no value in altering the course of the disease. The general effects of the larger doses do not appear significantly different from those observed with the usual therapeutic doses and do not justify the expense and dangers involved.

27. The Status of Certain Questions Concerning Vitamins, Reports of the Council on Pharmacy and Chemistry, J. A. M. A. **106:** 1732 (May 16) 1936; Condol and Ertron Not Acceptable for N. N. R., ibid. **109:** 132 (July 10) 1937.

Experiment and Then Think.—By 1850 Bernard's fame as an exponent of the experimental method in medicine began to be spread throughout Europe and overseas to the United States of America. At this time young physicians in America, as soon as they had taken their medical degrees, set out, if they were able, on the grand tour, and their principal objective was France rather than Germany. It is said that not only did they visit hospitals, their primary interest, but nearly all of them attended some of Bernard's lectures at the Collège de France, and a few engaged in experimentation under his direction. One of the best known American doctors of the nineteenth century, Weir Mitchell of Philadelphia, spent the year 1850-1851 in Paris, and, although he attended courses designed for surgical training, he wrote home that he liked Bernard's lectures in physiology and Robin's in microscopy much better. Bernard's pedagogical attitude is well illustrated in a conversation with Weir Mitchell. The latter had said that he thought so and so must be the case. "Why think," replied Bernard, "When you can experiment? Exhaust experiment and then think."—Olmsted, J. M. D.: Claude Bernard, Physiologist, New York, Harper & Bros., 1938.

SULFANILAMIDE IN THE TREATMENT OF BRAIN ABSCESS AND PREVENTION OF MENINGITIS

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The cure of a brain abscess and prevention of an almost certain hemolytic streptococcus meningitis by the administration of sulfanilamide has not been previously reported. Rowe [1] in a recent article describes two cases of brain abscess in which sulfanilamide constituted part of the therapy. The first patient had a pneumococcic (type V) abscess of the cerebellum which was treated also by surgical drainage and the administration of 220,000 units of appropriate pneumococcus antiserum. The second patient had a cerebellar abscess, culture of which revealed Friedländer's bacillus. The abscess was also treated by surgical drainage. As many instances of abscesses similar to these cured by drainage alone are known, as pneumococcus antiserum was used in case 1 and as sulfanilamide has not been shown to be effective against Friedländer's bacillus, as Rowe notes, it is impossible to credit sulfanilamide with the excellent result obtained in Rowe's cases.

In the case reported here the presence of a streptococcic cerebellar abscess was confirmed by culture of the pus obtained by aspiration, but the abscess was not drained. Furthermore the surface of the cerebellum, washed by cerebrospinal fluid and directly connected with the ventricular system and subarachnoid space, was contaminated with pus swarming with hemolytic streptococci. Certainly in the ordinary course of events a meningitis would have developed. Under sulfanilamide therapy there was no recurrence of symptoms attributable to the abscess, and no symptoms of meningitis ever appeared.

REPORT OF CASE

History.—F. S., a girl aged 4 years, referred to the University of Chicago Clinics by Dr. Joseph Brennemann of the Children's Memorial Hospital, was perfectly well until March 7, 1938, when she complained of a pain in her right ear. Her family physician was called. He prescribed some drops for instillation in the external auditory canal. The following day she had apparently completely recovered and continued to be well until March 29, when she suddenly complained of severe pain in her head. She vomited twice that evening. The pain and vomiting continued and she rapidly grew weak and was unable to walk. April 2 she was admitted to the Children's Memorial Hospital. There she was examined by a competent otologist, who could find no evidence of any disease in the ears. A lumbar puncture was made and the spinal fluid is reported to have contained 60 lymphocytes per cubic millimeter and 60 mg. of dextrose per hundred cubic centimeters. She was uncooperative and cried almost continuously. The head was retracted and drawn to the left so that the left ear almost touched the left shoulder. There was bilateral papilledema and deviation of the eyes to the left. All voluntary movements were ataxic, particularly those of the left extremities. A diagnosis of an expanding lesion in the left cerebellar hemisphere was made.

Examination.—She was transferred to the University of Chicago Clinics April 3 at 4 p. m. On admission here she was stuporous and cried out only when moved. The head was retracted and there was marked suboccipital tenderness. Definite early choking of the optic disks was present. The pupils were dilated and reacted poorly to light. The eyes were deviated to the left. The cranial nerves were otherwise normal.

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1. Rowe, S. N.: The Use of Sulfanilamide in the Treatment of Brain Abscess, Ann. Surg. **107:** 620-626 (April) 1938.