Further Experiences with △1, 9 Alpha Fluoro, 16 Alpha Hydroxyhydrocortisone (Triamcinolone) in Treatment of Patients with Rheumatoid Arthritis

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Cumulative observations concerning the use of triamcinolone in 74 patients with rheumatoid arthritis and in 15 with related rheumatic syndromes are reported. Anti-inflammatory properties of this steroid were confirmed. Although disturbances in electrolyte metabolism were not observed, the usual undesirable effects resulting from the administration of glucocorticoids were noted.

Es reportate observationes cumulative in re le uso de triamcinolona in 74 patientes con arthritis rheumatoide e in 15 patientes con syndromes rheumatic affin. Le qualitate anti-inflammatori de iste steroide esseva confirmate. Ben que disturbationes in le metabolismo electrolytic non esseva observate, le usual effectos adverse que resulta del administration de glucocorticoides esseva observate.

IN 1956, Bernstein and co-workers[1] announced the microbiologic synthesis of △1, 9 alpha fluoro, 16 alpha hydroxyhydrocortisone. In rat liver glycogen assays this exhibited glucocorticoid activity 15 to 36 times greater than hydrocortisone. In rat electrolyte assays the steroid caused no sodium retention. The significant feature of this compound is the presence of the 16 hydroxyl group (fig. 1), the addition of which appears to abolish the marked sodium-retaining property exhibited by other 9 alpha fluoro steroids, without diminishing their potent glucocorticoid activity.

A preliminary report of clinical and metabolic studies of this new steroid (triamcinolone) was made by Hellman and associates.[2] These early metabolic studies showed that this new steroid, administered as the diacetate salt to patients with rheumatoid arthritis for 21 days, caused little or no change in nitrogen, calcium, or potassium balances. Sodium balance became slightly negative in one patient. Antirheumatic activity was excellent, and the only major complication observed was the development of diabetes in one patient. Because these early metabolic and clinical results were very good, more extensive studies of this compound were undertaken. This report comprises a review of our experiences with this steroid used in the treatment of patients with rheumatic disease prior to June 15, 1957.

METHOD OF STUDY

Triamcinolone* has been administered to 89 volunteers with chronic rheumatic disease. All but five patients had rheumatoid arthritis, classic or a variant (table 1).

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TABLE 1.—*The Type of Rheumatic Disease in Patients Who Received Triamcinolone*

DIAGNOSIS	NUMBER
Rheumatoid arthritis, classic	74
Rheumatoid arthritis with psoriasis	3
Rheumatoid arthritis with rheumatoid syondylitis	3
Rheumatoid arthritis with osteoarthritis	4
Systemic lupus erythematosus	3
Nonarticular rheumatism	1
Palindromic rheumatism	1
Total	89

Most subjects were female. The ages ranged from 24 to 71 years, with the peak distribution in the sixth decade of life (table 2). The arthritis was classified according to the American Rheumatism Association Criteria[3] whenever possible. In most patients the disease was in Stage II or III, Class 2 or 3 (table 3). Many patients had been receiving another corticosteroid for many months just before triamcinolone was administered; in these patients the classification was affected by the antirheumatic activity of the previous therapy.

Treatment with triamcinolone was continued for less than 90 days in 38 patients (table 4). These patients are included in the study in order to permit complete analysis of reasons for discontinuing treatment. Fifty-one patients were treated longer than ninety days; 16, longer than 180 days; 6, for more than 270 days. The longest period of treatment was 315 days.

Usually triamcinolone was administered as the diacetate salt, acetylated at positions 16 and 21 (fig. 1). Table 5 shows the dose administered as the diacetate. During the last portion of this study many patients received the steroid as the pure alcohol in a dose calculated to be 84 per cent of the amount of diacetate previously used (the steroid percentage of the diacetate preparation).

The dosage of steroid to be administered was determined in various ways. To many patients who had been receiving prednisone or prednisolone, triamcinolone diacetate was given in the same dosage in order to contrast effects of equivalent doses of these steroids. In others who had been receiving prednisone, triamcinolone diacetate was given in the same dose and if the antirheumatic effect was found to be different, the dosage of triamcinolone was adjusted upward or downward until antirheumatic effects were judged to be comparable for each steroid. In still other patients, including those not previously treated with a steroid, triamcinolone was administered in the amount necessary to produce the desired antirheumatic effect. Arrived at in these ways, Table 5 shows that most of the patients received 6 to 18 mg. of triamcinolone diacetate daily; 51 patients received 6 to 12 mg. daily, and 20 patients were given 12 to 18 mg. daily. Four patients received 18 to 24 mg. of the steroid daily for more than 180 days.

TABLE 2.—*The Sex and Age of the Patients Studied*

	Male—17 patients			Female—72 patients		
Age (years)	20–29	30–39	40–49	50–59	60–69	70–79
Number of patients	3	8	18	34	21	5

TABLE 3.—*Classification of the Arthritis in the Rheumatoid Patients Studied*

Stage	I	II	III	IV
Number of patients	10	30	30	10
Class	One	Two	Three	Four
Number of patients	0	48	30	4

TABLE 4.—*Duration of Treatment*

Days	*Number of Patients*		
Less than 30	12		
30–60	14	38	
60–90	12		
90–120	12		
120–150	11	29	
150–180	6		
180–270		16	51
270–315		6	

RESULTS

Antirheumatic effects.—In the majority of patients the antirheumatic effect of this new steroid was very good and similar to that of other steroids possessing good anti-inflammatory properties. In almost all, partial suppression of rheumatoid activity which the patient and physician considered to be satisfactory was sustained on daily doses less than 12 mg. (table 5). In 13 patients, 6 mg. or less of the steroid, daily, provided good suppression of the disease. In more than half of the patients 6 to 12 mg. of triamcinolone diacetate were required daily for satisfactory benefit; only a few patients needed more than 18 mg., daily. As with other steroids, the amount of triamcinolone diacetate required for satisfactory benefit varied in direct proportion to the severity of the rheumatoid process. Some of the patients treated for the longest time required amounts among the largest doses used only because these patients (first chosen for this study) had severe arthritis, difficult to suppress. Only late in the study were patients with mild rheumatoid arthritis treated. This is the chief reason that the patients who received 3 to 6 mg. of triamcinolone diacetate daily were treated for less than 180 days.

Best results were obtained when the steroid was given in four relatively equal doses, five or six hours apart, beginning on arising. In only a few patients was it necessary to increase the daily dose during prolonged treatment in order to continue to obtain good benefit.

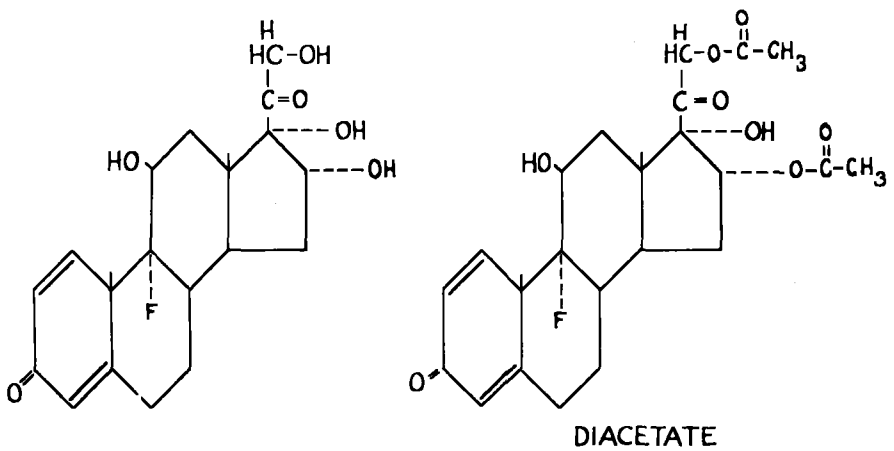

FIG. 1.—△1, 9 Alpha Fluoro, 16 Alpha Hydroxyhydrocortisone (Triamcinolone).

TABLE 5.—*Dose of Triamcinolone Diacetate Employed*

Daily Dose Range (mg.)		*Duration of Treatment* Days				Number of Patients
		Less than 90	90-180	180-270	270-315	
3–6	Number of Patients	10	3	0	0	13
6–12		21	17	9	4	51
12–18		6	9	4	1	20
18–24		1 (S.L.E.)	0	3	1	5
	Total					89

For nine patients who had not been receiving another corticosteroid just before commencing triamcinolone, and in whom treatment was continued for more than 90 days, in 7 instances the therapeutic effect (graded by the criteria of the American Rheumatism Association[3]) was grade 2 (impressive); in 2 instances it was grade 3 (unimpressive). In those patients who were not receiving another suppressive agent just before treatment with triamcinolone diacetate was begun there was usually an impressive reduction in the erythrocyte sedimentation rate (fig. 2).

The antirheumatic effect of triamcinolone may be compared with that of other corticosteroids in the 55 patients changed abruptly from prednisone (or prednisolone) to triamcinolone diacetate (table 6). For comparable antirheumatic benefits about half of these patients required less triamcinolone diacetate

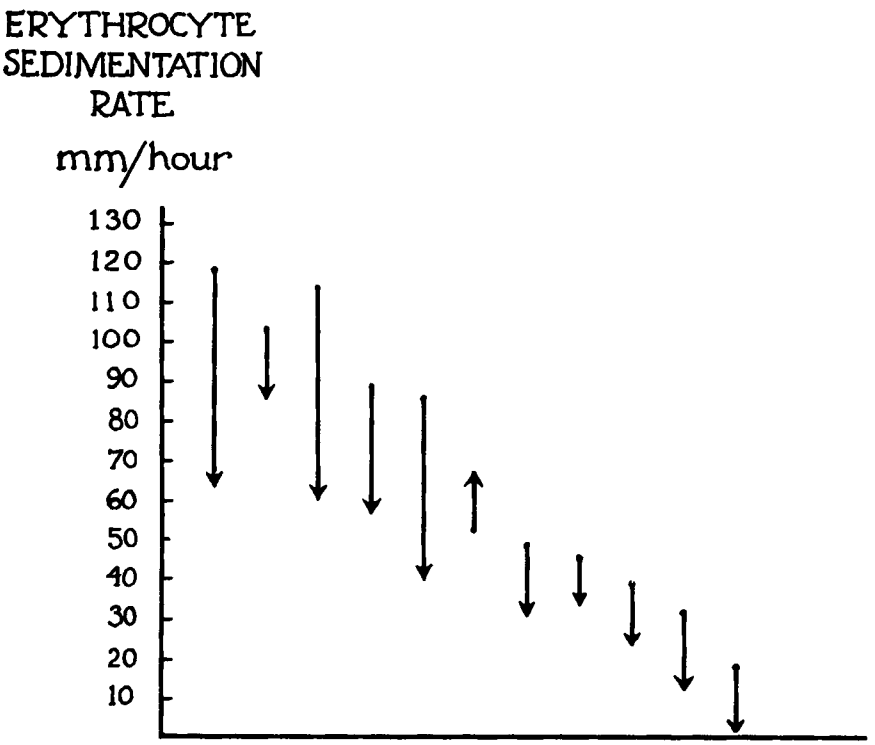

FIG. 2.—Erythrocyte sedimentation rate changes in 11 patients treated with triamcinolone diacetate.

TABLE 6.—*Comparative Antirheumatic Effect of Triamcinolone Diacetate and Prednisone (or Prednisolone)*

Of 55 patients changed from prednisone to triamcinolone diacetate,
27 patients required less triamcinolone diacetate for comparable antirheumatic effect.
2 required 55 per cent of the prednisone dose.
4 required 66 per cent of the prednisone dose.
21 required 80 per cent of the prednisone dose.
24 patients required equivalent amount of each steroid.
3 patients required 125 per cent of the prednisone dose.
Average Triamcinolone Diacetate Dose: 90 per cent of the prednisone dose

TABLE 7.—*Results of Intra-articular Injection of Triamcinolone Diacetate in Patients with Rheumatoid Arthritis*

Patient	*Joint injected*	*Number of injections*	*Dose (mg.)*	*Result*	*Comparison with effects of 50 mg. hydrocortisone*
O.M.	Knee	1	25	Excellent	—
S.O.	Knee	2	25	Good	Equal
E.W.	Knee	1	25	Good	—
M.S.	Knee	1	25	Good	Better
M.C.	Knee	2	25	Excellent	Equal
J.R.	Knee	1	25	Good	Equal
M.S.	Both Knees	1	25	Good	Better

than prednisone, but the difference in dose requirement was small in most patients. In about half of the patients equivalent amounts of prednisone and triamcinolone diacetate gave comparable antirheumatic effects. In only three patients was more triamcinolone diacetate required. The overall average dose of triamcinolone diacetate needed for comparable clinical benefit in these 55 patients was nearly the same as that of prednisone—90 per cent.

A significant local anti-inflammatory effect occurred in every instance that triamcinolone was injected intra-articularly in patients with rheumatoid arthritis (table 7). Twenty-five mg. of triamcinolone diacetate injected into the knee joint gave excellent results in three instances, and good results in seven. These results could be compared to the effects of intra-articular injection of 50 mg. of hydrocortisone suspension in five patients; in three patients in whom both knees were inflamed comparably, triamcinolone suspension was injected into one knee, and hydrocortisone was injected into the other knee on the same day; two other patients had previously received 50 mg. of hydrocortisone intra-articularly in the joint that was later injected with 25 mg. of triamcinolone diacetate. In three patients of these five the anti-inflammatory effect of the two steroids used intra-articularly was considered to be equal; in two patients effects of triamcinolone diacetate was judged to be better than hydrocortisone, although the differences were not great.*

In 14 patients triamcinolone (alcohol) was substituted for triamcinolone diacetate, and treatment was continued from 10 to 50 days; in five other patients corticosteroid treatment was started with triamcinolone alcohol. In

*Since these observations were summarized similar results have been obtained with intra-articular injection of triamcinolone diacetate in more than 50 additional patients.

all of these patients antirheumatic effect was good or excellent, and when comparison was possible, effects of the alcohol were considered comparable to those of the diacetate when given in doses containing equivalent amounts of the steroid (84 per cent of the diacetate).

Undesirable effects.—The value of any corticosteroid needs to be appraised not only on its merits but also on its demerits. For patients with rheumatoid arthritis, a *chronic* disease, the value of triamcinolone, as of other therapeutic agents, depends upon whether the drug can be tolerated without important undesirable effects, administered for a long time in doses adequate to effect a satisfactory antirheumatic response. In other words, the dose of a steroid required for good antirheumatic effect is important only when considered in relation to troublesome effects that may result when it is administered.

All undesirable effects observed during this study are listed in table 8. Twenty-three of 38 patients treated for less than 90 days had no side effect, whereas only eight of 51 patients treated for longer periods had no troubles. Two or more side effects often would occur in the same individual.

As expected from the results of the animal assays and the early metabolic studies, sodium retention did not occur and edema never developed in these patients as a result of administration of this steroid. Commonly, there was a sodium and water diuresis and loss of weight during the first few days of treatment. If edema had been present, it either disappeared or decreased significantly during this early period of treatment, when diuresis was commonly observed. If edema persisted it was reasonably explained on the basis of inadequate venous or lymph return flow, vascular obstruction or other me-

TABLE 8.—*Undesired Effects Observed when Triamcinolone was Administered to 89 Patients*

	38 patients treated less than 90 days	*51 patients treated longer than 90 days*
No undesired effects	23	8
Sodium retention, edema	0	0
Hypokalemia	0	0
Hypertension	0	0
Psychoses	0	0
Apprehension and insomnia	1 (?)	0
Depression, mild	1	4
[a]Headache, severe	1	2
[b]Dizziness	3	3
[c]Anorexia	6	2
[d]Nausea, G.I. distress	4	0
[e]Sleepiness	1	3
[f]Weakness, fatigue	4	7
[g]Erythema	1	5
Purpura, ecchymosis	1	16
Cushingoid facies	3	15
Diabetes	0	1
Osteoporosis, vertebral fracture	0	1
Peptic ulcer	reported in separate table	
[h]Weight loss	reported in separate table	

[a-h]Effects not commonly observed with other corticosteroids.

chanical factors. In more than 100 determinations of blood potassium done during prolonged treatment, hypokalemia was not observed, and there was no clinical manifestations of potassium deprivation. Elevation in blood pressure did not occur after commencing this steroid; if hypertension had been present, it often decreased after triamcinolone was administered. No psychoses occurred.

Apprehension and insomnia were listed as side effects of the drug in one patient; however, these troubles may not have been drug effects, for this psychoneurotic patient had similar complaints soon after commencing several other drugs (steroids or nonsteroids). She may have anticipated troubles; nevertheless, they are listed as "side effects" since the patient stopped taking triamcinolone on the third day of its use because of these symptoms. Five patients reported a sense of mild depression unaccompanied by any other emotional or psychic changes; in one instance this was encountered early; in four patients it was experienced several months after treatment began.

Several troubles, not commonly encountered during the use of other steroids, are considered unique effects of triamcinolone. In one patient severe headache occurred only 10 days after treatment began and persisted many days until the drug was stopped. A second trial was accompanied by headache within three days. In two other patients headache began later in treatment and persisted. Dizziness was very troublesome in six patients; it occurred in the three patients with severe headaches, and in three others without other troubles. Anorexia developed soon after commencing treatment in six patients; in two others it began later and persisted. Nausea and other vague gastrointestinal discomforts including bloating, distention, and mild diffuse abdominal pain occurred in four patients (without evidence of peptic ulcer). Troublesome sleepiness was complained of by four persons, in one instance early, and in three, later in treatment. Very disturbing weakness, tiredness and fatigue occurred in 11 patients; in four instances this occurred after 30 to 60 days of treatment but in seven, it was bothersome only after more than 90 days. Usually, these kinetic troubles were accompanied by anorexia and by significant weight loss.

Intense erythema of the face, neck and upper thorax developed and persisted in six patients; it began early in treatment in one patient, and after 90 days of therapy in five others. This resembled the "burn" from exposure to sunshine or ultraviolet light; it blanched under pressure, and appeared to be due to capillary dilation and congestion. Easy bruising, ecchymosis and purpura were frequently observed after prolonged treatment; in one instance it began during the second month of treatment. This complication was seen only when large doses of triamcinolone were used (more than 10 mg. daily), but was not strictly proportional to the daily dose.

As with all other glucocorticoids, prolonged use of triamcinolone frequently caused deposition of fat about the face, neck, supraclavicular regions and upper dorsal back, often with hypertrichosis and acneiform dermatitis, producing facies typical of Cushing's disease. These changes and the ecchymoses were observed in essentially the same degree and with the same frequency as seen during prolonged use of other $\triangle 1$ hydrocortisone preparations.

In six of 15 tests of glucose tolerance a mild diabetic curve was observed,

and in one patient (a latent diabetic) clinical diabetes developed. Fasting blood sugar values were normal in twenty patients tested at irregular but frequent intervals after prolonged triamcinolone treatment. Except in the patient who became diabetic, glycosuria did not occur. The glucocorticoid potency of triamcinolone, observed clinically, compares with that of other steroids possessing good antirheumatic properties.

Four patients with severe osteoporosis who had compression fractures of one or more vertebral bodies during other steroid therapy were placed on triamcinolone therapy. In none of these did roentgenograms show an increase in osteoporosis, and no new fractures occurred in these patients treated up to 180 days. In another patient who had received hydrocortisone for one year, prednisolone for one and a half years, and then triamcinolone, fresh compression fractures of the bodies of vertebrae D12, L2 and L5 occurred 100 days after using triamcinolone, 12 to 16 mg. daily.*

Circumstances concerning the discontinuance of triamcinolone are presented in table 9. Six patients could not continue under our supervision for various reasons not relating to their illness; in all of these patients the antirheumatic effect was good. One patient died of breast carcinoma 100 days after receiving 16 mg. of triamcinolone daily with good benefit. Three patients judged this new steroid, taken in doses of 6 to 18 mg. daily, to be of too little value to continue, and therefore discontinued treatment after 10, 21 and 35 days respectively. In one patient apprehension, "nervousness" and insomnia developed immediately after beginning to use triamcinolone in a daily dose of only 8 mg.; because of these troubles she stopped treatment on the third day. Similar symtoms had occurred when other new treatments had been initiated. In all other patients in whom triamcinolone was discontinued for various troubles antirheumatic effect was very good. In two patients poor appetite, nausea, headache and vertigo were so annoying that treatment was stopped after a short trial. Two other patients had persistent severe headache and dizziness, for which reasons treatment was stopped after 45 and 155 days respectively. In one of these patients a second trial of the steroid was attended by the same troubles. Peptic ulcer was the basis for stopping treatment in three patients; in each, triamcinolone was administered when it was known that an ulcer was present, having developed while receiving other corticosteroid therapy previously. Because of significantly increased indigestion the steroid was discontinued in two of these three patients on the 35th and 185th day of treatment respectively. In the third patient, treatment was stopped on the 55th day after a massive hemorrhage occurred, even though relief and suppression of the arthritis was greater than had been experienced from any of several other steroids used previously. One patient developed clinical diabetes which became apparent on the 45th day of treatment; however, triamcinolone was administered until the 190th

*After this manuscript was prepared a new vertebral fracture developed in one of these patients (female) on the 276th day of treatment while receiving 12 mg. of triamcinolone daily. In addition one male patient, aged 67 years, who received no other steroid preceding its use, had treatment with triamcinolone in doses beginning with 24 mg. daily, slowly reduced to 6 mg. daily. On the 305th day of treatment two vertebrae were fractured; roentgenograms showed osteoporosis of the spine.

TABLE 9.—*Reasons for Discontinuing Triamcinolone*

Number of Patients	*Reasons*	*Duration of Treatment* days	*Daily Dose* (mg.)	*Antirheumatic Effect*
6	Left our supervisory treatment	10–212	5–18	Good
1	Died—carcinoma	100	16	Good
3	Insufficient symptomatic relief	10, 21, 35	6–18	Poor
1	Apprehension, nervousness, insomnia	3	8	Fair
2	Anorexia, nausea, headache, dizziness	21, 28	8, 12	Good
2	Headache, dizziness	45, 155	10	Good
2	Peptic ulcer, increased distress	35, 185	8, 10	Good
1	Peptic ulcer, hemorrhage	55	8	Excel.
1	Diabetes	190	8–14	Good
4	Anorexia, weight loss, weakness, sleepiness	75–200	12–18	Good —2 Excel. —2

23 of 89 patients treated; in 3 because of poor antirheumatic effect, in 13 because of troublesome side effects.

day in order to study this metabolic complication. After cessation of treatment the diabetes again became latent and the rheumatoid activity worsened considerably. In four patients anorexia, loss of weight, weakness and sleepiness were of such magnitude that triamcinolone was discontinued even though antirheumatic effects were good or excellent. Among all 89 patients studied triamcinolone was stopped in 23 – because of poor antirheumatic effect in only three instances, and as a result of troublesome complications in 13 patients. In about half of these patients troubles occurred early in treatment; in the remainder, after prolonged administration of the steroid.

TABLE 10.—*Instances of Considerable Loss of Body Weight during Triamcinolone Treatment*

Patient	*Duration of Treatment* days	*Daily dose* mg.	*Weight Loss* Pounds	%
F.M.M.	35	16	10	7
E.G. (ulcer)	35	8	12	8
G.S.	60	16	6	6
R.A.	70	18	10	7
M.R.	90	8	8	6
F.W.	95	14	30	17
R.S. (ulcer)	120	10	17	14
J.J.	170	10–12	16	12
L.C. (ulcer)	180	8–10	8	6
*A.L.	190	8–10	15	11
F.F.	195	12–14	11	8
*M.S. (C.F., edema, infection)	200	12	26	21
F.M.	210	22	8	7
*R.D.	250	10	12	9
G.G.	280	10	9	7

Total—15 of 89 patients (11 without complicating disease); 11 of 51 patients were treated longer than 90 days; 8 of these had no complicating disease.

*Weight loss graphically shown in figure 3.

The loss of three to five pounds of body weight occurred in most patients the first few days of treatment, when urine volume was greater and increased sodium excretion had been observed in early metabolic studies. In most patients the weight became relatively stable seven to 10 days after starting triamcinolone; however, in 15 of the 89 patients studied, slow weight loss continued (table 10). In the first four patients listed in table 10 gradual loss of weight reached 6 to 8 per cent of the beginning weight in a relatively short period of time. In the remaining 11 patients whose weight loss is tabulated (table 10) the rate of reduction was slower but became significant after 90 or more days of treatment. In patients E.G., R.S., and L.C. an active peptic ulcer very likely contributed to the weight loss and in M.S. congestive heart failure existing at the outset of treatment and later a febrile respiratory infection undoubtedly added considerably to the total loss which in 200 days was 26 pounds, 21 per cent of the original weight. In all other patients listed, 11 of the 89 studied, and eight of 51 treated longer than 90 days, no complicating illness existed to contribute to weight loss which in some instances was as much as 9, 12 and 17 per cent of the beginning weight (R.D., J.J., and F.W.).

Examples of this loss of body weight are shown in figure 3. In each instance the initial rapid loss followed by a slower loss during the remaining months of treatment is evident.

All of the patients who lost considerable weight received 10 or more milli-

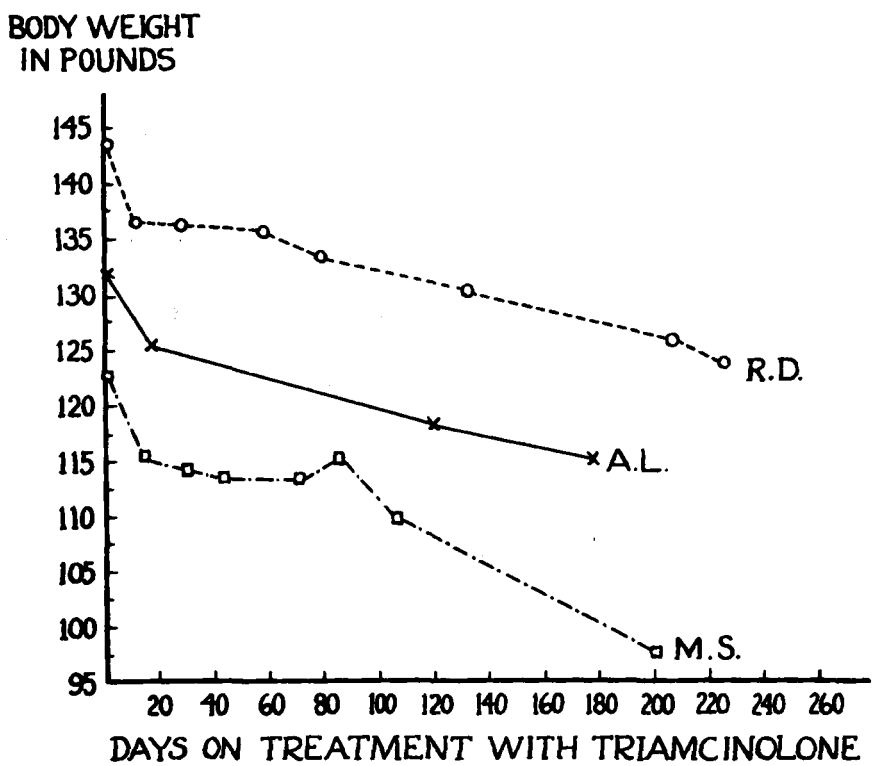

FIG. 3.—Changes in body weight of three patients on prolonged triamcinolone therapy.

grams of triamcinolone daily, some more than 15 mg.; many had poor appetites and ate less than usual; some felt weak and tired easily, were "light-headed" or dizzy and had headache and sleepiness. In a few of these patients the skin was loose, dry and wrinkled and much wasting of sucutaneous tissue and muscle was apparent.

Of much interest are the changes and events in the group of patients who had peptic ulcer (table 11). In 19 patients in whom peptic ulcer had developed while they were receiving another corticosteroid, and who had continued to receive corticosteroid therapy after the ulcer was known, treatment was changed to triamcinolone diacetate. All of these patients were females and ranged in age from 36 to 71 years. All were treated with a regimen of bland diet, antacids, anticholinergic drugs and some with bed rest. In three of these patients we were unable to obtain follow-up gastrointestinal roentgenograms, but they remained free of gastrointestinal symptoms and had guaiac-negative feces during treatment lasting 30, 60 and 150 days respectively. In two patients partial gastrectomy had been performed two and three years previously; thereafter each continued to receive large doses of hydrocortisone or prednisolone before triamcinolone was commenced. Each has remained without ulcer symptoms, and roentgenograms have been negative repeatedly during the 180 and 270 days of treatment with triamcinolone. In two other patients the ulcer had healed before triamcinolone was commenced; throughout treatment they remained free of ulcer symptoms, and roentgenograms after 90 and 120 days of treatment showed no ulcer. In 12 patients active ulceration had continued during treatment with another corticosteroid and was present when triamcinolone was commenced. In five instances, after prolonged triamcinolone treatment, active ulceration continued; in two, the ulcer appeared unchanged in roentgenograms after 75 and 180 days; in three, the ulcer was larger, and in one of these hemorrhage occurred. In seven patients the ulcer became asymptomatic and in six of these roentgenograms showed complete healing after 120 to 210 days of treatment; in one, the ulcer healed rather quickly but became reacti-

TABLE 11.—*Events and Clinical Course Regarding Peptic Ulcer in 20 Rheumatoid Patients Treated with Triamcinolone*

19 patients had had peptic ulcer before triamcinolone administration, all female.

Age: years	36	40–49	50–59	60–69	71
No. of pts.	1	3	9	4	2

	Clinical Course regarding Peptic Ulcer	*Stage of Treatment* (days)
3	—unknown—no follow-up roentgen studies possible, asymptomatic	30, 60, 150
2	—partial gastrectomy had been performed 2 and 3 years previously, continued asymptomatic; X-ray negative	180, 270
2	—healed before triamcinolone started—continued healed	90, 120
12	—continued active ulceration when transferred to triamcinolone	
	2 unchanged	75, 180
	3 larger; hemorrhage, perforation	100, 180, 190
	7 healed during triamcinolone	120 to 210 (6)
	1 reactivated	75
1	peptic ulcer developed during triamcinolone therapy	45
20	Total	

vated. Only one new ulcer was demonstrated among the remaining 70 patients while receiving triamcinolone. This was in a male patient, 59 years of age, who had been treated for a year with prednisolone and then changed to triamcinolone. At the beginning of treatment with the new steroid he had no ulcer symptoms; roentgenograms were not made then. After 30 days of triamcinolone therapy indigestion began and on the 45th day a gastric ulcer was demonstrated.*

All other patients treated longer than 90 days (36 patients, not including those listed in table 11) had no clinical indication of peptic ulcer and gastrointestinal x-rays in 20 of these patients showed no ulcer.

Discussion

The antirheumatic effect of triamcinolone is usually excellent when used systemically, either as the diacetate or as the alcohol, and when injected intra-articularly good anti-inflammatory benefits result. Only three patients considered this new steroid less beneficial than other corticosteroids. Administered in an equal weight dose in many patients it was more potent than other corticosteroids previously used. There were personal differences in response, but the over-all average requirement of triamcinolone diacetate was 90 per cent of that of prednisone for comparable antirheumatic effects.†

Many of the undesirable effects of this new steroid are comparable to those of previously prepared glucocorticosteroids. Localized fat deposition resulting in altered body configuration, skin changes, hypertrichosis and Cushingoid facies occurred as with other potent steroids. Purpura occurred in essentially the same incidence and severity as observed with prednisone and prednisolone. Triamcinolone may be expected to precipitate clinical diabetes if it exists in latent form because of its potent glucocorticoid property.

Some distinctly advantageous features appear to characterize triamcinolone. It has no sodium-retaining property: hence edema is not induced by its administration. This attribute is advantageous if a steroid is to be administered to an edematous patient. Metabolic studies showed that sodium diuresis and sometimes a negative sodium balance result from administration of triamcinolone. This sodium diuresis and reduction of tissue hydration accounts for initial weight loss during early use of this steroid. If sodium excretion continues for prolonged periods, troublesome dehydration may result. Lack of sodium retention may be an important reason that hypertension did not result from

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*Since preparation of this manuscript this new ulcer continued to remain unhealed roentgenographically although asymptomatic for 5 months.

Another new peptic ulcer developed in one of the 89 patients herein reported on, 240 days after starting treatment with triamcinolone. The ulcer was "silent," until it perforated and required surgical treatment. The patient was a female aged 58 years who had had continuous corticosteroid therapy with different steroids for six years, without ulcer symptoms and with two negative gastrointestinal roentgenograms prior to the use of triamcinolone.

†Of the preparation of triamcinolone now available for prescription use the average dose would approximate 80 per cent of the dose of prednisone for comparable antirheumatic effects.

treatment with triamcinolone, and why existing hypertension sometimes was reduced. It was considered advantageous that hypokalemia, excessive euphoria, excitement and psychoses did not occur.

Some undesirable effects occurred not commonly observed with use of other steroids; these, therefore, may be peculiar to triamcinolone. Headache, dizziness, troublesome "light-headedness" and sleepiness were complained of and in some instances required cessation of the use of this steroid. The erythema occasionally seen on the face, neck, hands and forearms appears to be due to capillary congestion. Nausea and indigestion occasionally noted early during use of triamcinolone are troubles not commonly encountered during use of other corticosteroids. A voracious appetite never occurred. When the appetite was affected it was lessened and sometimes became very poor so that in these patients there was inadequate food consumption.

The weight loss which sometimes occurred slowly after initial water loss was of special interest. Some of these patients also had complained of anorexia, lack of ambition, ease of fatigue, light-headedness, sleepiness and sometimes headache. Dry wrinkled skin and sparse subcutaneous tissue suggested chronic dehydration, and muscle atrophy was considerable. Early metabolism studies[2] showed no significant nitrogen loss. More metabolic investigations were conducted on some patients observed in the course of our clinical studies who were not previously subjects of balance studies. In these later investigations larger daily doses of triamcinolone than used in some of the early studies were employed. It was found that when 24 mg. or more of the steroid were given daily when there was only moderate protein intake for many days, some patients had greater nitrogen loss than during control periods; sodium diuresis was the rule; potassium balance was not significantly disturbed; a loss of calcium was observed in four instances. Although the early experiences did not show it, the results of these later metabolic studies are interpreted to indicate that this steroid *can* be catabolic, especially if administered in large doses for prolonged periods. The progressive weight loss and accompanying symptoms seen in some of our patients may result from some or all of the following factors, added to the initial sodium and water diuresis: (1) poor appetite leading to reduced consumption of food, (2) some catabolism of protein tissue, (3) chronic dehydration. When more investigations of the pathways and mechanisms of metabolism of the new synthetic steroids have been elucidated and compared to the behavior of naturally occurring corticosteroids in the human body, these clinical effects will be better understood.

Because of the favorable differences in the balance studies done with triamcinolone, as contrasted with the effects of other steroids, it was hoped that pathologic fractures from osteoporosis and peptic ulcers might not occur with prolonged use of triamcinolone. This hope was not realized. One patient* developed new compression fractures of vertebral bodies, and one new gastric ulcer* developed while triamcinolone was being used; however, both of

*Since this summary was made, a second patient of this group also had multiple vertebral compression fractures, and two additional patients developed peptic ulcer.

these patients had previously received another potent corticosteroid for long periods before triamcinolone was begun. It is encouraging that of 12 patients with active peptic ulcer in whom triamcinolone was used to replace another steroid, the ulcer healed in seven patients, all of whom received a usual ulcer regimen of diet and antacids; in one patient, the ulcer later became active. Thus, healing occurred in 50 per cent of the patients with known active ulcer while receiving triamcinolone. It is well known that ulcers have healed while the patient has received other steroids, too. Only longer study in more patients will reveal the true relationship of this new steroid to the problem of peptic ulcer, and differences from other steroids, if differences exist.

These studies indicate that triamcinolone is another corticosteroid possessing potent antirheumatic effects and certain differences in other physiologic properties. With several antirheumatic corticosteroids now existing, and others expected to appear, the physician must exercise careful selection of the steroid best suited to the clinical circumstances in each patient. Examples: triamcinolone would be expected to be preferable to hydrocortisone in an edematous patient or in an overweight individual whose appetite is stimulated undesirably by other steroids. Triamcinolone may be undesirable for an undernourished patient who continues to lose weight and requires a large amount of steroid for satisfactory antirheumatic benefits. It may be that administration of a mixture of steroids, each contributing separate advantages in some patients, may be preferable to the use of only one. For instance, an undernourished rheumatoid patient who is edematous might be better managed by supplying half of his steroid requirement as prednisone to get better stimulation of appetite and euphoria, and half as triamcinolone to minimize sodium retention and edema. Such selective use of steroids is now being investigated.

Summary

Experiences with the prolonged administration of △1, 9 alpha fluoro, 16 alpha hydroxyhydrocortisone (triamcinolone) to a large group of patients with rheumatoid arthritis have been reviewed. Triamcinolone was found to have practical therapeutic usefulness in patients with rheumatoid arthritis. This new steroid possesses a very high order of antirheumatic potency in both systemic and local use. Differences in some of the other effects of this new steroid, compared with other available steroids, are in most circumstances favorable when contemplating prolonged use of a corticosteroid. Absence of sodium-retaining property permits its use even when edema exists. Other advantages of this steroid have been discussed. Some undesired effects commonly encountered with other corticosteroids occurred with triamcinolone; other side effects which appear to be peculiar to triamcinolone have been reviewed.

Complete knowledge of the metabolism, therapeutic value and problems that may arise during prolonged aministration of this new synthetic steroid in patients with rheumatic disease will be known only after further studies in more patients.

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