Systemic Lupus Erythematosus

Results of Treatment with Triamcinolone

EDMUND L. DUBOIS, *M.D.*, Los Angeles

• Twenty-nine patients with systemic lupus erythematosus were treated with a new synthetic unsaturated prednisolone derivative, triamcinolone, for as long as 11 months. This hormone is 1.3 times as powerful as prednisone and 4.4 times more potent than hydrocortisone as an anti-inflammatory agent. The average dose for beginning therapy in cases of mild systemic lupus erythematosus was 20.6 mg. a day. The average maintenance dose used to control mild exacerbations of the disease was 26.0 mg. a day. There was no evidence of sodium retention or potassium loss.

Sixteen patients had upper gastrointestinal x-ray studies before and during therapy with triamcinolone. There was no evidence of peptic ulceration except in one patient who was receiving 96 mg. a day. Nine patients had gastric analysis with histamine before and during therapy. No significant changes were noted in results of these tests, even in the patient who had an ulcer. No abnormal increase in uropepsin was noted in cases in which this factor was tested.

The pattern of clinical improvement closely paralleled that obtained by previous treatment with older steroids. There was a disappearance of all the clinical and laboratory abnormalities produced by the disease, with the exception of long standing renal involvement. A major difference between triamcinolone and other steroids was a tendency to progressive gradual loss of weight, partly owing to fluid loss. Cushingoid appearance produced by other steroid therapy did not disappear.

The cutaneous side effects, particularly Cushingoid appearance, hirsutism and striae were more pronounced than with older steroids. The most serious side effect was muscle weakness which appeared in six patients, all women, in from four to thirty-two weeks after starting triamcinolone. The profound muscle weakness, most pronounced in the quadriceps group, gradually cleared after several weeks of therapy with another steroid.

Fourteen patients had received prior steroid therapy with all the older anti-inflammatory hormones and seven of them were better controlled and felt better with triamcinolone.

THE PROBLEMS OF THERAPY in systemic lupus erythematosus have been under study at the Los Angeles County General Hospital for some eight years. During that time 275 patients with various forms of the disease have been treated with salicylates, antimalarial drugs and steroids.[5,6,7]

For the 11 months preceding the preparation of this report the author had opportunity to study a group of 29 patients with systemic lupus erythematosus requiring steroid therapy who were being treated with a new synthetic fluorinated, unsaturated anti-inflammatory hormone, triamcinolone (Aristocort®). Chemically, this substance is 9 alpha fluoro —16 alpha hydroxy-delta one hydrocortisone.[1,2] The purposes of this report are two: One is to review our experiences with this new agent and compare the results to that produced by older steroids, and the other is to present the data obtained from routine gastrointestinal roentgenograms, gastric analysis, and 24-hour urinary uropepsin determinations before and during treatment with this new steroid in order to assay its ulcerogenic tendency and effects on gastric secretions.

Chemical Configuration

Chart 1 illustrates the structure of triamcinolone alcohol compared to that of some of the older steroids. During the earlier part of the study the diacetate ester was utilized (acetate radical on carbons 16 and 21). The structure of the alcoholic form is similar to that of prednisolone with the addition of a fluorine atom at the 9 alpha position and a hydroxyl group at the 16 alpha position (see Chart 1). Fluorination greatly increases both the mineral corticoid and glucocorticoid effects of all steroids; however, the salt-retaining effect is relatively much more increased. With the addition of a hydroxyl group at carbon 16 there is again elimination of the sodium-retaining effect of fluorination without much loss of the increased anti-inflammatory potency.[1,2]

Clinical Material

Twenty-nine patients with active systemic lupus erythematosus were treated. The diagnosis was

From the Department of Internal Medicine, the University of Southern California School of Medicine, and the Los Angeles County General Hospital, Los Angeles 33.

Supported by a grant from Lederle Laboratories, the Attending Staff Association of the Los Angeles County General Hospital and the National Lupus Erythematosus Foundation Inc.

Triamcinolone (Aristocort®) was generously supplied by Dr. Christopher H. Demos of Lederle Laboratories.

Presented before the Section on Internal Medicine at the 87th Annual Session of the California Medical Association, Los Angeles, April 27 to 30, 1958.

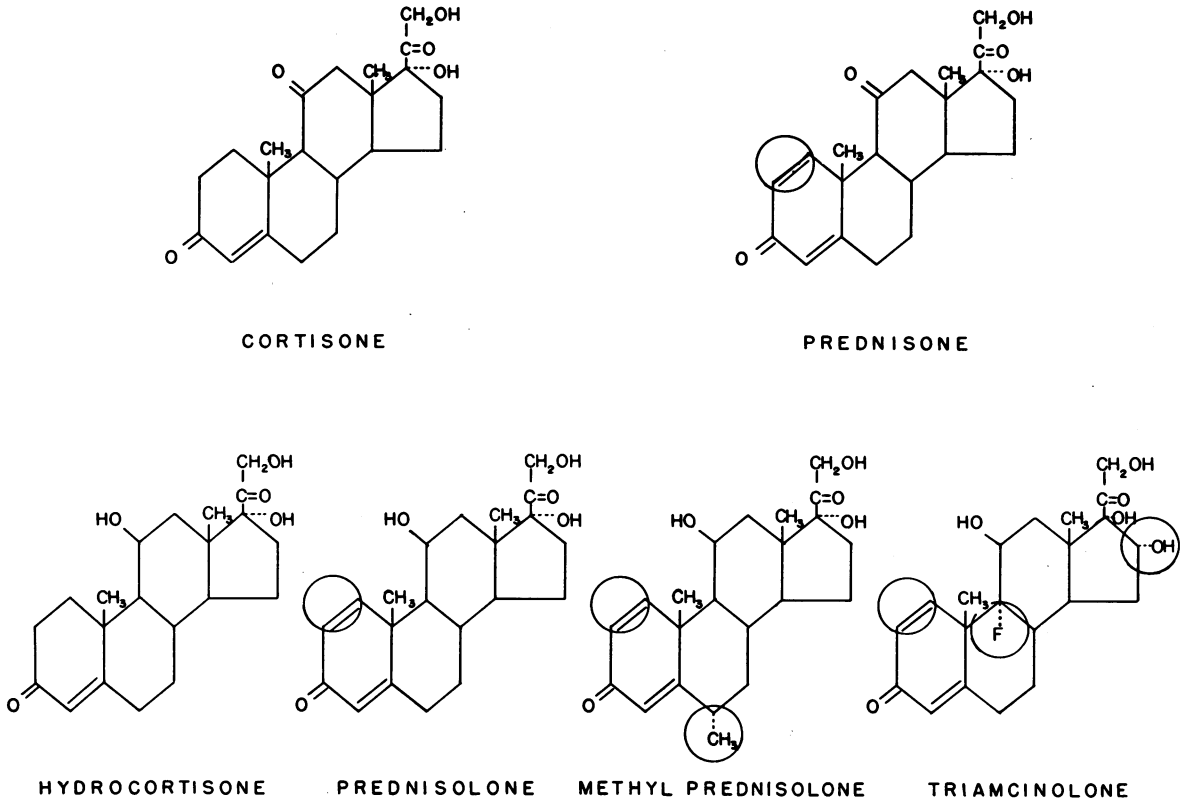

Chart 1.—Configuration of triamcinolone as compared with some of the older steroids.

proven by the observation of L.E. cells in 25 cases, by clinical features and skin biopsy in three cases, and was made on the basis of clinical features alone in one case. There were 22 females and seven males (see Table 1). The average duration of illness from the time of onset of disease to the time of the writing of this paper was 92 months. Four patients were well stabilized by administration of steroids at the time of transfer to triamcinolone and 14 were having exacerbation of varying severity. Eleven patients had active disease and had not recently received other steroidal therapy. The average age of these patients at the time of treatment was 33.7 years with a median of 32.0 years. The average age at which illness had begun was 26.0 years. The mean duration of total hormone therapy including triamcinolone was 28.2 months and the median was identical. The duration of treatment with triamcinolone averaged 4.3 months with a median of four months and a range of four days to a maximum of 10.5 months in two patients. The total experience was 125.2 patient-months of therapy (see Table 2).

TABLE 1.—*Clinical Material (29 Cases)*

	Number	Per Cent
Males	7	29
Females	22	76
Diagnosis originally confirmed by:		
L.E. cells	25	86
Clinical pictures and biopsy	3	11
Clinical picture alone	1	3

Principles of Steroid Therapy

Once the diagnosis of systemic lupus erythematosus is made, the type of treatment instituted depends entirely on the clinical severity of the illness. If the presence of the disease becomes known as a result of a false-positive serologic test for syphilis in an asymptomatic patient who has perhaps a few L.E. cells, then no therapy is necessary other than close observation of the patient. If the main complaint is mild rheumatoid arthritis or rheumatic fever-like symptoms, this often can adequately be controlled by modified bed rest and salicylates, which should be increased to the point of salicylism. The frequent use of these drugs should be encouraged since they reduce the requirements for anti-malarial drugs and steroids. None of the patients studied had allergic reaction to them. Increased bed rest, in addition to other treatment, is usually helpful in controlling symptoms in the active stages of the disease. If salicylates and rest fail, or if cutaneous lesions are present, then anti-malarial therapy should be instituted.[5] When both these measures are

TABLE 2.—*Clinical Data on the 29 Cases of S.L.E. Treated With Triamcinolone*

	Range	Median	Mean
Age in years (at time of therapy)	11-57	32.0	33.7
Duration of disease in months to time of writing	6-240	78	92
Duration of all steroid treatment including triamcinolone (months)	1-80	27.0	28.2
Triamcinolone therapy (months) *	0.2-10.5	4.0	4.3
Dosages (mg. per day):			
Initial treatment (11 cases)	4-40	18	20.6
Maintenance (26 cases) †	8-96	18	26.0
Triamcinolone therapeutic ratio‡:			
×hydrocortisone (9 cases)	1.0-7.5	4.5	4.4
×prednisone (5 cases)	0.75-3.3	1.2	1.3
×prednisolone (1 case)	1.0	.....	.....
×cortisone (1 case)	3.1	.....	.....

*Total patient-months of therapy was 125.2.

†The majority of these patients had active S.L.E. not well controlled by other steroids at the time of transfer to triamcinolone. This explains the larger maintenance doses. Most of the patients initially treated with triamcinolone did not require large doses of anti-inflammatory hormones.

‡Therapeutic ratio=Amount of drug required to produce equal anti-inflammatory effects on a milligram for milligram basis. This is determined by dividing the amount of triamcinolone required for maintenance into the amount of older steroids. In order to ascertain the dosage of triamcinolone to use in transferring from another steroid, divide the therapeutic ratio into one: for example, with hydrocortisone the therapeutic ratio is 4.4, then the factor is $1 \div 4.4 = 0.23$ (or 23% of) the dose of hydrocortisone.

inadequate, or if the patient either is critically ill or has neurological or renal involvement, steroid treatment should be started.

The principles involved in using triamcinolone are identical with those used in therapy with older agents.[5,6,7] If there is no clinical improvement, (which is best judged by the temperature response in the acute cases in 24 to 48 hours) then the dose of steroids should be increased by amounts of 25 to 100 per cent, depending upon the urgency of the situation, until therapeutic response occurs. As much as 3,500 mg. of cortisone per day has been used in treating an acute exacerbation of lupus with a successful outcome. There are no fixed limits of the dosage required to produce remissions; however, in several cases in which there was no clinical response after several days' treatment with 3,500 mg. of cortisone per day (or the equivalent in other steroids) increasing the dose beyond this point did not help and the patients died.

It is no longer necessary with the newer unsaturated steroids to routinely induce overt Cushingoid changes in the first 14 days of treatment.[7] If neurological disease due to vascular systemic lupus erythematosus is present, much larger doses should be used and a Cushingoid appearance induced as quickly as possible in order to block progression of this change and initiate healing, which usually occurs.

Once the patient is afebrile and the symptoms controlled, the amount of medication must not be reduced until there is general improvement in the laboratory changes as well as the clinical picture of the patient. It is advisable to continue high dosages of steroids until all the abnormal physical findings, such as pleural effusion, pericarditis with effusion and other active evidences of inflammation, subside. Advanced renal disease is the one exception; it will not be benefited by continued use of large amounts of these hormones. Acute toxic nephritis with elevation of the nonprotein nitrogen to approximately 100 mg. per 100 cc. will usually benefit from steroids, particularly if hypertension is absent. The nephrotic syndrome due to systemic lupus erythematosus will often improve. If there is no improvement in the renal lesions after two months of adequate steroid therapy with production of a Cushing state, then other modes of treatment such as nitrogen mustard must be considered.[5]

When the hemoglobin level has become almost normal and the abnormal physical features have disappeared, the steroid dose is reduced by decrements of about 10 per cent. There should be a waiting period of four to seven days or longer to observe signs of relapse. Mild exacerbations with slight return of symptoms often appear within 24 hours—the so-called rebound phenomenon. This subsides spontaneously in a few days without increase in dosage if the amount of steroid being given has not been reduced below the critical maintenance level, permitting real relapse to occur.

The clinical condition and the hemoglobin content are used as the major guides to steroid therapy. If significant renal involvement is present, this condition is closely watched in order to determine when to reduce the dose. The sedimentation rate is never used as the main index to dosage, since it can remain indefinitely accelerated in some patients despite complete clinical remissions in which no steroid administration is necessary. The L.E. cell test is helpful in gauging the overall progress of the disease but should not be used as a basis to determine therapy since it requires several weeks for changes to occur, and many patients have persistently positive L.E. cell tests even when the disease is in remission requiring no medication.

Dosage

The amount of steroid required varied entirely with the severity of the disease and the sensitivity of the patient to the therapeutic agent.[5,6,7] In the case of the 11 patients who had received no previous therapy, attempt was made to estimate from past experience what the initial dosage ought to be. In making the estimate we assumed, from animal experiment and previous human studies, that the potency of triamcinolone was a little greater than that of prednisolone or prednisone.[4] The starting doses in these cases varied, from the addition of 4

mg. per day to the therapeutic regimen of a 19-year-old boy with mild arthritis which was poorly controlled by salicylates and anti-malarial drugs, to a maximum of 40 mg. per day in three patients with very active disease and multisystem involvement. The estimation of dosages in nine of the eleven cases on the basis of clinical experience and severity of the illness was correct and required little modification for control of the exacerbations.

Five patients who had been taking prednisone were changed to triamcinolone. The dosage required for the same clinical effect was four-fifths the amount of prednisone; in other words, the new steroid had a therapeutic potency 1.3 times that of prednisone on a milligram basis. The range varied from being 0.75 times as potent as prednisone to being 3.3 times as powerful (see Table 2).

Nine patients with varying degrees of control of the disease while taking hydrocortisone were changed to triamcinolone. The amount of the new steroid for equivalent maintenance was 0.23 times the dosage of hydrocortisone, or, conversely, the potency of triamcinolone was 4.4 times that of hydrocortisone on a milligram basis. The range in individual cases varied from 1.0 to 7.5 times as potent.

One patient was changed from prednisolone, 20 mg. per day, to triamcinolone, 20 mg. per day, with equally good control. In another case a severe exacerbation of the disease prevented a determination of dosage equivalents. An additional patient was changed from cortisone, 50 mg. a day to triamcinolone, 16 mg. a day, with good control.

Ten patients during the course of treatment were changed from triamcinolone acetate to the alcohol without any difference being noted in the clinical effects. Theoretically, the alcohol is a 17 per cent smaller molecule and should have been slightly more potent on a milligram basis.

Adjuvant Therapy

All patients were permitted a normal intake of salt except four who had a problem with excessive edema due to renal involvement. They were placed on a 200 mg. sodium diet. Except for one patient in whom a trace of ankle edema developed during triamcinolone therapy, there was no evidence of sodium retention. Supplementary potassium was not given. Low serum potassium was not detected even in patients receiving a maximum dosage of 96 mg. a day.

A routine regimen of prophylaxis against gastric ulcer, such as is usually recommended for patients taking over 50 mg. of cortisone per day or its equivalent, was not used in the present series except when indicated.[5,6] An "ulcer diet" and administration of anticholinergic drugs were continued in two patients who had recent history of duodenal ulcer. Two other patients who had epigastric distress from other steroids were also on a similar diet. Gastrointestinal roentgen series, uropepsin concentrations and gastric analyses in these patients remained normal. Three additional patients received anticholinergic drugs (but were not given an ulcer diet) because of epigastric distress following steroid therapy. The previously mentioned gastrointestinal studies on these patients were normal and remained so.

Gastrointestinal Studies

Sixteen patients had upper gastrointestinal x-ray examination before and every one or two months while under treatment. The dose of triamcinolone in these cases varied from 4 mg. a day to as much as 96 mg. a day. One patient was known to have an active duodenal ulcer, proven roentgenographically, before triamcinolone therapy. The patient followed an "ulcer regimen" while taking the new steroid and the lesion healed. In one patient who was not following a regimen for prophylaxis against ulcer, an acute superficial duodenal ulcer developed, with gross bright red blood in the stool, during a three weeks period of administration of 96 mg. of triamcinolone daily. This occurred during the sixth month of high dosage steroid therapy. Without reducing the dose of triamcinolone, vigorous ulcer regimen was carried out and the lesion healed. Because of a lack of general improvement despite a Cushingoid appearance, a month after the bleeding episode a change was made to 6a-methyl prednisolone, 96 mg. a day, and anticholinergic drugs were discontinued. Ten days later a similar bleeding episode occurred; it abated upon reinstitution of anticholinergic therapy and reduction of the dose of 6a-methyl prednisolone. Two weeks later the patient died and at autopsy evidence of disseminated cryptococcus was observed, as well as changes of systemic lupus erythematosus. No evidence of gastrointestinal ulceration was found at post-mortem examination. In the other cases no abnormalities were noted roentgenographically during the course of treatment with the new steroid. Bunim[3] reported a 22 per cent incidence of new peptic ulcers in patients who were similarly treated with prednisteroids and were not following an ulcer prophylaxis regimen.

Gastric analysis was done in nine patients before and every two months during treatment with triamcinolone. Free and total acidity were determined before and after subcutaneous injection of histamine phosphate, 0.1 mg. per 10 kg. of body weight. Specimens were drawn every 10 minutes after administration of histamine for a total of 40 minutes. No significant changes were noted in any of the

patients, including the one who had a proven duodenal ulcer which was healing under therapy and the patient in whom an acute ulcer developed.

Twenty-four-hour uropepsin determinations were performed by the method of West in which the normal range is 15 to 40 units per hour.[14] Gray and co-workers[9] and Spiro[13] observed that excretion of uropepsin is increased with steroid or corticotropin (ACTH) therapy but other investigators[12] did not confirm this finding. Thirteen patients who received triamcinolone were studied as to uropepsin excretion before and every few months during therapy. No significant changes were noted in any of them, including the one in whom an acute ulcer developed. Results were all within the normal range throughout the study in seven patients. In three patients, including one who received 32 mg. a day for five months, uropepsin excretion was below the normal range before and throughout steroid therapy. In three patients, including the one with healing peptic ulcer, it rose from subnormal to normal levels during therapy.

Results of Therapy

The pattern of clinical improvement closely paralleled that obtained in systemic lupus erythematosus by previous treatment with corticotropin and the other anti-inflammatory hormones. The fever abated in 24 to 48 hours, joint pains disappeared in several days and pleural effusion and cutaneous lesions subsided in one to two weeks. Retinal changes, anemia, adenopathy and cachexia gradually improved over a period of several weeks. Renal abnormalities, including proteinuria, sediment changes and nitrogen retention of short duration, often returned to normal during steroid-induced remissions. The long standing renal lesions, particularly those associated with hypertension, are unaffected by hormonal therapy but seem to be helped by nitrogen mustard.[5,6] Two patients had a severe nephrotic syndrome of systemic lupus erythematosus with uremia and hypertension. Both were unaffected by doses of triamcinolone as high as 80 mg. a day. One patient with a mild nephrotic syndrome did not have diuresis with the new steroid but had an excellent diuresis from nitrogen mustard. Another patient with low grade nephropathy showed no change.

In 18 patients there was a decrease in weight, averaging 10.7 pounds with a median of 9 pounds and a maximum of 18 pounds. The average loss in terms of per cent of initial body weight was 7.8 with a median of 8.2 (see Table 3). The change was usually gradual and progressive over months rather than acute during the first few days of change to the new steroid. If there was much edema of nonrenal origin, this disappeared within a week. Cushingoid appearance induced by other steroids did not abate. The decrease in weight is apparently owing to a combination of several factors: One is a complete lack of sodium retention with this steroid, even less than with prednisone; another, a great deal less appetite stimulation, the least of any of the steroids currently available; a third factor is muscle wasting due to probable negative nitrogen balance, which will be discussed below. In six patients, all females, there was definite overt atrophy of muscles of the extremities and pronounced weakness along with increased Cushingoid appearance. This change did not occur in any of the seven males in the series who were on equally large doses of triamcinolone.

TABLE 3.—*Clinical and Laboratory Changes Produced by Triamcinolone*

CLINICAL CHANGES	Median	Mean
Weight:		
Decreased (18 cases) (pounds), range 6 to 18 pounds	9.0	10.7
Decreased (loss in per cent of initial body weight), range 3.8 to 13.5	8.2	7.8
Unchanged (8 cases).		
Increased (3 cases), range 3 to 29 pounds	....	13.3
Blood Pressure (mean pressure, mm. mercury):		
Unchanged in 20 cases.		
Decreased (4 cases)	....	23.0
Increased (5 cases)	....	29.0
LABORATORY CHANGES		
Hemoglobin (grams):		
Unchanged in 16 cases.		
Decreased (3 cases)	....	1.1
Increased (10 cases)	2.2	2.7
White cell count (thous./mm.^{3}):		
Unchanged in 19 cases.		
Decreased (0 cases).		
Increased (10 cases)	5.0	4.1
Sedimentation rate (Wintrobe):		
Unchanged in 10 cases.		
Decreased (9 cases)	23.0	23.7
Increased (4 cases)	....	28.0
Inadequate data (6 cases).		
L.E. cells (rotary method):		
Unchanged in 5 cases.		
Decreased in 7 cases.		
Disappeared fully in 4 cases.		
Increased in 2 cases.		
Remained absent in 7 cases.		
Inadequate data in 4 cases.		

Weight increased in three patients, one man gaining 29 pounds after six weeks of therapy, and was unchanged in eight patients. Edema of one plus appeared in one patient—this despite a loss of weight. There was no evidence of a low sodium syndrome or potassium depletion clinically or by electrolyte determinations. Tests were performed whenever any symptoms appeared possibly related to these changes.

The mean blood pressure was unchanged in 20 cases. It decreased an average of 23 mm. (mercury)

in four cases and increased an average of 29 mm. in five cases. Two of the five patients with increase in pressure had uremia.

Changes in Laboratory Observations

Details of changes that occurred in results of laboratory determinations during therapy are shown in Table 3. The hemoglobin increased in ten cases, the increase averaging 2.7 gm. per 100 cc. with a median of 2.2 gm. A slight decrease occurred in three cases, the average decline being 1.1 gm. In 16 instances the hemoglobin was unchanged. In 14 of the patients the hemoglobin had already been elevated to a normal range by previous steroid treatment.

The leukocyte content increased an average of 5,060 per cu. mm. in ten cases, with a median of 4,100. It was unchanged in 19 instances, and in no case did it decrease.

The sedimentation rate (Wintrobe) decreased in nine patients an average of 23.7 mm. in one hour with a median of 23. It increased in four cases an average of 28 mm. There was inadequate data in six cases.

L.E. cell tests performed by the rotary technique demonstrated a decrease in positivity in seven cases and an increase in two cases.[8] The cells fully disappeared in four patients within a minimum of four weeks. L.E. cells were unchanged in five cases and remained absent throughout therapy in seven patients, five of whom had had L.E. cells before previous therapy. In four cases data was inadequate.

Side Effects

The most serious side effect of triamcinolone was muscle weakness. With this steroid also is associated greater severity of cutaneous changes such as Cushingoid appearance, acne, hirsutism and striae than occurred with older hormones of this type. There has been no problem with mineral corticoid effects such as salt retention or hypertension except as noted above.

The side effects of triamcinolone as compared with those of prednisone and prednisolone are shown in Table 4. Only five patients in the triamcinolone treated group had the benefits of prednisteroid therapy before they began taking the newer hormone. Hence the two groups are somewhat comparable, for they either were untreated before the use of steroids was begun or had been treated with cortisone or hydrocortisone for the most part. The incidence of Cushingoid appearance with moon face was quite similar in both groups. Severe hirsutism was noted in 21 per cent or six cases of the triamcinolone treated group as against 3 per cent in the prednisteroid group. Hirsutism appeared within four weeks on doses of triamcinolone as low as 16 mg. a day and was much more pronounced than the author observed with the older steroids. At times the entire forehead was covered with hair. No excessive hirsutism of this type was found in males. The medication was stopped in one patient because of hirsutism. Striae and ecchymoses were more severe and common with the newer steroid, being prominent in 14 per cent of cases, as against 3 per cent with prednisteroids. Edema accumulated in only one of the patients receiving triamcinolone and in 6 per cent of the prednisteroid group.

Two patients treated with triamcinolone noted epigastric burning after taking the hormone. In one case the burning abated when the patient ingested an antacid preparation for several weeks while receiving the steroid, and in the other case it spontaneously disappeared. In neither patient was there significant change in the conditions observed in the gastrointestinal studies previously discussed. One patient in the prednisteroid series developed similar epigastric symptoms despite a prophylactic ulcer regimen; one patient on triamcinolone, as noted above, developed an acute peptic ulcer. Routine prophylactic ulcer therapy was not employed in the

TABLE 4.—*Side Effects of Triamcinolone Compared With Those in a Similar Series of Patients Treated with Prednisone and Prednisolone*

	No. Cases in Patients Receiving Triamcinolone	Per Cent	Per Cent on Prednisone or Prednisolone*
CUSHINGOID APPEARANCE			
After transfer from older steroids:			
Increased	4	14	12
Decreased	0	0	5
Unchanged	4	14	17
Initial appearance after starting triamcinolone as first steroid	4	14	15
Initial appearance after transfer to triamcinolone from other steroids	1	3	0
None at any time while receiving triamcinolone	16	55	51
Total number who developed or maintained Cushingoid features	13	42	42
OTHER SIDE EFFECTS			
Pronounced hirsutism	6	21	3
Acne	5	17	16
Striae (marked)	4	14	3
Ecchymoses (marked)	4	14	3
Edema	0	0	6
Muscle weakness†	6	19	0
Diabetes mellitus (severe)	0	0	6
Epigastric distress	2	6	3
Peptic ulcer‡	1	3	3

*Data from the author's comparable series of 37 cases treated with prednisone or prednisolone.[6] The patients in this series had previously been treated with hydrocortisone, cortisone and corticotropin. Fifteen of these patients subsequently had triamcinolone.

†Occasionally profound leg weakness may occur in active systemic lupus erythematosus due to spinal cord or peripheral nerve vascular involvement. This is quite rare and usually responds well to increased steroid therapy.

‡The patients on triamcinolone were not on a prophylactic ulcer regimen whereas all those on prednisone or prednisolone had been.

triamcinolone series, whereas it was in the prednisteroid group.

The most serious side effect of triamcinolone therapy was the appearance of profound muscle weakness, particularly in the extensor muscles of the legs and occasionally in the deep back muscles. The patients were characteristically unable to rise from a chair without using their hands or climb stairs without holding the bannister. They could not rise from a squatting position unaided. These symptoms appeared in from four weeks to as long as 32 weeks after therapy was begun. The average time of appearance was 13 weeks with a median of five weeks. The lowest dose at which it appeared was 12 mg. a day. There did not appear to be a relationship between the largest doses and the development of this side effect.

The onset of this change was quite insidious but when fully developed it was profound and necessitated cessation of the steroid in all six cases. It did not occur in males. In all cases the development of weakness seemed to be preceded by a severe Cushingoid appearance with definite atrophy of the extremity muscles. Weakness in the upper extremity was not as evident as in the lower. Electrolyte studies in four cases showed the serum sodium and potassium to be normal. Two patients were changed to prednisone and four to hydrocortisone in equivalent dosages. About two weeks after the change, their strength gradually began to return to normal. One of the patients had transitory paresthesia for one day in her legs and she could have had primary weakness due to vascular systemic lupus erythematosus. None of the other patients had any sensory changes. Reflexes were intact and active in the legs. These changes were similar to the quadriceps weakness seen in hyperthyroidism and myasthenia gravis.

Case 1 below illustrates the appearance of muscle weakness while the patient was receiving triamcinolone as well as refractoriness of the renal lesion to diuresis without the aid of nitrogen mustard.

Case 1. A 31-year-old Chinese housewife became ill in March, 1954, with butterfly area rash, loss of weight, arthralgia and pleuritic pain. Upon biopsy of a specimen of skin lupus erythematosus was diagnosed and the patient was given cortisone, 75 mg. a day, with only moderate relief of symptoms. When first examined by the author, in November 1954, the patient was slightly Cushingoid. Blood pressure was 150/85 mm. of mercury. A grade II blowing systolic murmur was present in the pulmonic area. There was no edema. The patient had normocytic anemia, the hemoglobin content being 11.2 gm. per 100 cc. The sedimentation rate (Wintrobe) was 56 mm. in one hour. The reaction of the L.E. cell preparation was 4 plus. Upon urinalysis, 4 plus albuminuria was noted. The urinary sediment contained many hyaline and granular casts and oval fat bodies. Urinary protein excretion was 8.5 gm. in 24 hours. Blood urea nitrogen content was 42 mg. per 100 cc. and cholesterol 280 mg. per 100 cc. Phenolsulfonphthalein clearance was 26 per cent in 15 minutes and in 2 hours was 77 per cent. Hydrocortisone, 20 mg. four times daily, was substituted for the cortisone the patient had been taking, and 20 mg. of nitrogen mustard was given intravenously. By February, 1955, there had been no change in the urine, although the blood urea nitrogen had decreased to 26 mg. per 100 cc. Another 20 mg. of nitrogen mustard was given. During the following two months, albuminuria decreased to 2 plus and there was a decided decrease in abnormal elements in the urinary sediment. There were about 30 erythrocytes per high power field and no casts. As the Cushingoid appearance continued, a change was made to prednisone from hydrocortisone but the appearance did not change. By May of 1956, the patient was asymptomatic and results of urinalysis were unchanged. All steroids were discontinued. In November, 1956, gross hematuria suddenly appeared. Morning periorbital edema and low grade fever were present. There were red cells and granular casts in the urine. Blood urea nitrogen was 45 mg. per 100 cc. and cholesterol, 160 mg. Prednisone, 80 mg. a day, was begun and diuresis lowered the body weight by 6 pounds. After four days the urine returned to normal in color and the number of erythrocytes returned to the previous level of 40 per high power field. In May, 1957, the patient felt well and again all steroids were discontinued. The albumin reaction of the urine was 1 to 2 plus, and moderate numbers of red cells and casts of various types were noted.

On October 29, 1957, the patient noticed increasing periorbital edema in the morning and definite ankle edema. The blood urea nitrogen was 26 mg. per 100 cc. The urinary protein reaction was 4 plus. Triamcinolone was begun, 10 mg. four times daily. By November 9 the ankle edema had increased to 2 plus and a dry cough began. Striae on the feet from the edema and administration of steroids were noted. The urinary protein reaction decreased to 1 plus. Because of progressive gain in weight and edema, chlorothiazide (Diuril) 1.0 gm. twice daily was added but without much response. Three days later the dose of the diuretic was increased to 1.0 gm. four times daily and still there was no reduction in weight. At this time the blood urea nitrogen was 46 mg. per 100 cc. and the cholesterol content 617 mg. per 100 cc. On November 14, 1957, 20 mg. of mustard was given intravenously. Within two days the body weight decreased 4 pounds, and in the next 12 days another 15 pounds. On November 19 the dose of chlorothiazide was reduced to 0.5 four times daily, then was omitted completely the following week. This diuretic had no apparent effect on the edema. On November 29 the blood urea nitrogen was 29 mg. per 100 cc. and only a trace of edema

remained. At about this time the patient noticed the insidious onset of muscle weakness; she was unable to rise from a chair without using her hands to lift herself. During the next few weeks weakness progressed to the point that the patient could not climb stairs without pulling herself up on the bannister. When examined again on December 10, she had become decidedly Cushingoid, with apparent atrophy of arm and thigh muscles. She was completely unable to rise from a chair without using her arms. When asked to rise from a squatting position, she collapsed to the floor and was unable to lift herself without help. Triamcinolone, which was being given at the rate of 32 mg. a day, was discontinued and prednisone, 20 mg. a day, was begun. (Although serum electrolytes were not determined in this case, serum electrolytes, including potassium, were within normal limits in four of the six patients in whom these tests could be done.) In the ensuing three weeks the patient had gradual improvement of strength and finally could rise from a chair unaided. Because of persistent urinary abnormalities, with rise in albuminuria to 4 plus, the dose of prednisone was increased to 40 mg. a day. During the following week the ankle edema increased to 2 plus. The weakness did not return although the patient continued to receive this larger dose for an additional three weeks.

Case Summary

In the foregoing case profound muscle weakness appeared six weeks after the administration of triamcinolone was begun and disappeared gradually three weeks after a change was made to prednisone in equivalent doses. The patient had received cortisone, hydrocortisone and prednisone in equally high doses previously and weakness had not developed. Also in this case the effectiveness of nitrogen mustard as a diuretic agent was demonstrated, the drug bringing about amelioration of the renal lesion of lupus after steroids and chlorothiazide failed. In addition, the benefit of steroids in acute glomerulonephritis due to systemic lupus erythematosus was shown.

DISCUSSION

Triamcinolone seems to have a definite place among the anti-inflammatory agents. It has less sodium-retaining property than other steroids currently available. It has no significant gastrointestinal stimulating activity, which should make it useful in patients who have had problems with peptic ulceration on older steroids. The development of an acute duodenal ulcer in one of the patients in the present series without changes in the gastric analysis and uropepsin excretion suggests that the mechanism of ulceration of the stomach and duodenum may not be related to acid or pepsin secretion but be caused by other factors such as a decrease in viscosity of gastric mucus or perhaps retardation of normal healing by the steroids.[10,11]

Many patients are helped more by triamcinolone than by the older steroids. Fourteen of the patients in the present study had received previous therapy with all the older anti-inflammatory hormones and seven of them were better controlled and felt better with triamcinolone than with previous steroids. Male patients showed no Cushingoid features while receiving this steroid, even in doses as high as 48 mg. per day for six weeks. In men triamcinolone may be the agent of choice.

The most serious side effect of triamcinolone in systemic lupus erythematosus is muscle weakness. It was observed in about 10 per cent of rheumatoid arthritic patients.[4] In that series it was of only minor degree, but the dosages used were smaller than those given in the present series. It is noteworthy that in the present series muscle weakness did not occur in males, possibly due to the protective action of testosterone against the protein catabolic action of triamcinolone.

Triamcinolone has more cutaneous side effects than the older hormones, hence would not be the one of choice for beginning therapy in the average patient.

Another disadvantage of this agent is that it, like the rest of the unsaturated steroids, varies greatly in potency from patient to patient. In some cases these hormones are of the same potency as hydrocortisone on a milligram basis, and in others they are ten times as powerful. Because of this great variability in dosage and individual unpredictability of action, I prefer to begin treatment in the average case of systemic lupus erythematosus with hydrocortisone unless there is a problem of cardiorenal disease.

435 North Bedford Drive, Beverly Hills.

ACKNOWLEDGMENT

The author is indebted to George Jacobson, M.D., professor of radiology, University of Southern California Medical School, for the assistance of his department in obtaining the gastrointestinal series, and for the technical assistance of Miss Alice Ohtomo and Mrs. Catherine Hawkins.

REFERENCES

1. Bernstein, S., Lenhard, R. H., Allen, W. S., Heller, M., Littell, R., Stoller, S. M., Feldman, L. I., and Blank, R. H.: 16-hydroxylated steroids, communications to the editor, J. Am. Chem. Soc., 78:5693, 1956.

2. Bernstein, S.: In press. Recent progress in hormone research, Proc. Laurentian Hormone Conference.

3. Bollet, A. J., Black, R., and Bunim, J. J.: Major undesirable side effects resulting from prednisolone and prednisone, J.A.M.A., 158:459-463, June 11, 1955.

4. Demos, C.: Personal communication, Lederle Laboratories.

5. Dubois, E. L.: Systemic lupus erythematosus: Recent advances in its diagnosis and treatment, Ann. Int. Med., 45:163-184, August 1956.

6. Dubois, E. L.: Prednisone and prednisolone in the treatment of systemic lupus erythematosus. J.A.M.A., 161: 427-433, June 2, 1956.

7. Dubois, E. L., Commons, R. R., Starr, P., Stein, C. S., Jr., and Morrison, R.: Corticotropin and cortisone treatment for systemic lupus erythematosus, J.A.M.A., 149:995-1002, July 12, 1952.

8. Dubois, E. L., and Freeman, V.: A comparative evaluation of the sensitivity of the L. E. Cell Test performed simultaneously by different methods, Blood, 12:657-670, July, 1957.

9. Gray, S. J., Ramsey, C., Reifenstein, R. W., and Benson, J. A., Jr.: The significance of hormonal factors in the pathogenesis of peptic ulcer, Gastro., 25:156-172, 1953.

10. Hirschowitz, B. I., Streeten, D. H. P., London, J., and Pollar, H. M.: The effects of eight-hour intravenous infusion of ACTH and the adrenocortical steroids in normal man. 1. Basal gastric secretion and plasma and urinary pepsinogen, J. Clin. Inv., 36:1171, 1957.

11. Janowitz, H. D., Weinstein, V. A., Sher, R. G., Cereghini, J. F., and Hollander, F.: The effect of cortisone and corticotropin on the healing of gastric ulcers: An experimental study, Gastro., 34:11-23, Jan., 1958.

12. Kirsner, J. B.: Drug induced peptic ulcer, Ann. Int. Med., 47:666-699, Oct., 1957.

13. Spiro, H. M., Reifehstein, R. W., and Gray, S. J.: The effect of adrenocorticotropic hormone on uropepsin excretion, J. Lab. & Clin. Med., 35:899-910, 1950.

14. West, P. M., Ellis, F. W., and Scott, B. L.: A simplified method for determining the excretion rate of uropepsin, J. Lab. & Clin. Med., 39:159-162, 1952.

For Your Patients—A number of specialists have asked that a slight copy change be made in Message No. 1. This has been done and now Message No. 1A is available as well as Message No. 1.

A Personal Message to YOU:

I consider it both a privilege and a matter of duty to be available in case of an emergency. However, you can understand that there are times when I may not be on call. I might be at a medical meeting outside the city, on a bit of a vacation—or even ill.

Consequently, I thought it would be a good precaution if—on this gummed paper which you can paste in your telephone book or in your medicine cabinet—I listed numbers where I can be reached at all times. Also, the number of a capable associate as an added service. Here they are:

_____	_____	_____
OFFICE	HOME	MY DOCTOR
_____	_____	_____
OFFICE	HOME	ASSOCIATE DOCTOR

Sincerely,

_____, M.D.

MESSAGE NO. 1A. Attractive, postcard-size leaflets printed on gummed paper, you to fill in telephone numbers and your signature. Available in any quantity, at no charge, as another service to CMA members. Please order by Message Number from CMA, PR Department, 450 Sutter, San Francisco.