patient can appreciate pin-prick as sharp, the burn is partial-thickness skin loss only, and it will heal without grafting in less than three weeks and leave no scar. The converse is *not* always true: if the burn is analgesic to pin-prick the burn is not necessarily full-thickness skin loss. It is either deep partial- or full-thickness skin loss. Even this knowledge is valuable to the surgeon. The skin in some regions, such as the dorsum of the hand or foot, heals badly after deep partial burning. In such cases excision and replacement with a thick split skin graft may be better.

There are exceptions to the sensitivity test. The face and scalp, and the palms and soles, have epithelial elements penetrating more deeply into the subcutaneous tissue than other parts of the body, and the pin-prick test should never be used in these areas. Similarly, it should not be used where the burn has been produced by chemicals, such as phenol, which have an analgesic action. It goes without saying that this test, like all the others mentioned earlier, should never be used in isolation, but in conjunction with knowledge of the anatomy of the skin and the history of the burn.

Yet another valuable sign in diagnosing the depth of necrosis when excising a deep burn is the red fat in the deeper part of the zone of stasis. This fat is dead. For three or four days after burning the zone of stasis in the skin and fat remains red, but after this time the red cells packing the capillaries lyse, and the avascular fat once more becomes white and difficult to distinguish from the normal fat beneath it.

Summary

The diagnostic problems of burns are discussed in this paper in the order in which they are usually encountered clinically.

The patient requiring resuscitation with colloid infusion may be diagnosed by the proportion of skin surface burned.

The amount and rate of colloid infusion may be assessed from hour to hour by following the changing trend of five clinical guides taken together—the general condition of the patient, the haematocrit level, the urine output, a formula, and measurement of the blood volume.

Whether blood transfusion is required depends on the degree of red-cell destruction. Although this varies greatly from case to case, both in amount and in time, it may also be assessed by five guiding factors—visible blood loss, evidence in a blood film, signs of shock with a normal haematocrit level, a falling haematocrit level without over-infusion, and direct measurement of the red-cell volume.

A routine is suggested for the early diagnosis of renal insufficiency; this needs to be differentiated from the physiological oliguria which accompanies oligaemia in the shock stage, or dehydration in the subsequent week. Oliguric and non-oliguric types of renal failure must also be distinguished if appropriate treatment is to be given.

The two criteria for suspecting electrolyte imbalance and for making daily blood chemistry examinations are renal insufficiency and failure to start oral feeding on the second day. Some suggestions are made for avoiding serious deficit or excess.

The rationale behind frequent bacteriological examination of the burn flora is given, and the early diagnosis of invasive infection and the choice of local treatment for the burn are discussed.

Finally, in connexion with the diagnosis of the depth of burning, the deceptiveness of appearance and the value of sensitivity to pin-prick as a sign of partial-thickness skin loss are emphasized.

Constant reassessment of the changing condition of the patient is an essential feature of successful burns treatment. Sometimes it can be measured, sometimes it must be an informed guess; but always the surgeon must be seeking to forestall the likely complications and to recognize in time their small beginnings.

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PREDNISOLONE TRIMETHYLACETATE IN INTRA-ARTICULAR THERAPY

BY

W. R. MURDOCH, M.B., F.R.F.P.S., M.R.C.P.Ed.
Medical Registrar, Glasgow Royal Infirmary

AND

G. WILL, M.B., B.Sc., F.R.F.P.S.
Senior Medical Registrar, Glasgow Royal Infirmary

Since the introduction of the steroids there has been a renewed interest in intra-articular therapy. The compound most often used has been hydrocortisone, and there is a voluminous literature on its effects. Those authors who have carried out controlled trials (Dixon and Bywaters, 1953; Hollander, 1953; Duff *et al.*, 1955; Duff, 1956; Fearnley *et al.*, 1956) are in agreement that hydrocortisone produces symptomatic benefit in many cases, but several authors have found this to be variable. Thus Robinson *et al.* (1955) obtained worth-while benefit in only half of the joints, although treatment was combined with special orthopaedic and physical therapy measures. Duff (1956) gained worth-while benefit of 7 to 10 days' duration on the average in 50% of cases, while in 31% response was poor, and there was no significant response in 19%. Sairanen (1956) obtained the best results in finger-joints. In the knee-joints the results were poor in 44%. Increased benefit was not obtained by large doses of up to 100 mg. or from repeated injections at short intervals. He concluded that new products with a prolonged effect would doubtless be the solution.

The desirable compound for intra-articular therapy is one with a marked anti-inflammatory action but low solubility. In this way an effective local concentration will be maintained for a prolonged period with little systemic absorption. A number of compounds have been derived from prednisone and prednisolone, the delta-1 derivatives of cortisone and hydrocortisone respectively, which have on systemic administration a greater anti-inflammatory activity than that of the parent substances. As prednisolone is the corresponding compound to hydrocortisone it would appear to be the more suitable for intra-articular therapy. The acetate esters of these compounds are of low solubility. The use of suspensions of crystals of fixed dimensions further delays solution. From a very large number of esters of prednisone and prednisolone investigated,

prednisolone trimethylacetate (Vischer *et al.*, 1955) was shown by Desaulles and Meier (1957), using animal experiments, to be the most suitable for local use.

The Investigation

An investigation of the value of prednisolone trimethylacetate in arthritis was undertaken. Knee-joints were used as they are comparatively easy to enter, and we could be reasonably certain of obtaining a number of specimens of synovial fluid from each knee. Results were assessed according to the relief of pain and the improvement in swelling. A study was also made of the cytological and biochemical changes of the joint fluid.

A total of 290 aspirations were carried out in 57 joints. The number of patients was 35—27 (44 joints) had active rheumatoid arthritis, 6 (9 joints) had osteoarthritis with marked radiological changes and severe symptoms, and 2 (4 joints) had recurrent hydrarthrosis. Of the 35 patients 23 were admitted to the wards for the initial period of treatment, and were subsequently seen at regular intervals as out-patients. The remaining 12 were treated entirely as out-patients. During the period of investigation the simple analgesics which the patients had previously been taking were continued, but no other treatment, in particular steroids or physiotherapy, was given. During their stay in hospital they were ambulant. As most of the patients were under close observation in the ward, and as their treatment was otherwise unchanged, apart from the use of prednisolone trimethylacetate, we feel that our results give a more accurate picture of the effects of the drug.

The knee-joints were entered from the lateral aspect at the level of the upper border of the patella. The skin was prepared with cetrimide and spirit. Dry sterile syringes and needles were used. The operators' hands were scrubbed, and a sterile towel was placed below the knee. A weal was raised with lignocaine ("xylocaine") 2%, using a fine needle, and a small quantity (approximately 0.5 ml.) was infiltrated into the tissues. A 10-ml. syringe and serum needle was then used for aspirating the joint. In a few cases, mainly osteoarthritis, where entry proved difficult, a lumbar puncture needle was used. It was not our practice to drain the joint. Usually a small amount (3–5 ml.), enough to permit routine analysis, was removed. The drug was supplied in 1-ml. ampoules containing 10 mg. of a microcrystalline suspension of prednisolone trimethylacetate. We used 20 mg. (2 ml.) as a standard dose. The interval between injections was initially seven days, until effusion had resolved. Thereafter further injections were gradually spaced out and eventually stopped. The number of injections given per joint varied from 2 to 12, with an average of 5.1. The average period of follow-up since the last injection has been 6.1 months.

We have previously commented on the difficulty of measuring changes in joint size accurately (Currie and Will, 1950). Although joint measurements were made, we found it more suitable to tabulate the results into four grades: marked effusion (+++); moderate effusion (++); slight effusion, where there was patellar tap only (+); and no effusion (0). Pain was assessed by arbitrary groups; severe (+++), moderate (++), mild (+), and absent (0). The initial status of the patients with regard to pain and effusion is shown in Table I.

TABLE I.—*Degree of Effusion and Pain Before Treatment*

Grade	Rheumatoid Arthritis		Osteo-arthritis		Recurrent Hydrarthrosis	
	Swelling	Pain	Swelling	Pain	Swelling	Pain
+++	24	19	6	7	4	2
++	17	24	3	2	—	—
+	3	1	—	—	—	—
0	—	—	—	—	—	2

Results

We had been warned by the manufacturers that there might be some local reaction to the injection, with temporary increase in pain. This occurred in only 2 of the 35 patients and persisted for only a few hours, to be followed by relief. The usual response was relief of pain beginning within six hours of injection, and becoming complete within 48 to 72 hours. Resolution of swelling, although consistent, was less rapid and usually required several injections. In the bilateral effusions the two joints always responded similarly to the drug. It is of value to discuss the results under the disease classifications.

Rheumatoid Arthritis

The most rapid relief of pain and swelling was obtained in this group, whose general features are summarized in Table II. Assessment at the end of the follow-up period shows the results to have been good in 23 (85.2%), fair in 2 (7.4%), in that regular maintenance injections have been required, and poor in two (7.4%).

TABLE II.—*Details of 27 Patients With Rheumatoid Arthritis*

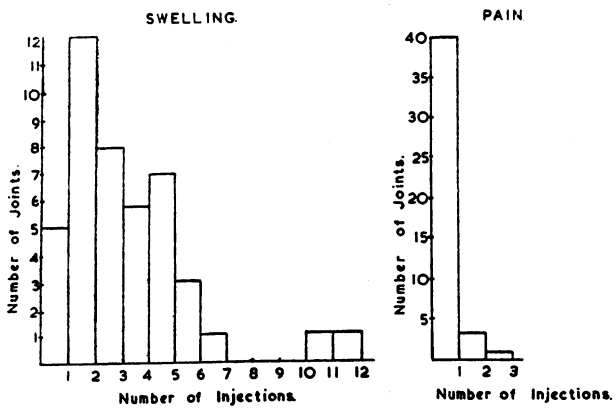
Case No.	Sex and Age	Duration in Years	E.S.R. mm./1 hr.	Nodules	Joints Involved
1	F 56	6	44	—	Wrists, knees, fingers
2	F 47	8	39	—	Knuckles, fingers, elbows, knees, ankles, feet
3	F 55	12	66	—	Wrists, fingers, elbows, knees, ankles
4	F 45	7	22	—	Fingers, wrists, knees, ankles
5	F 66	8	16	—	Fingers, wrists, knees
6	F 36	8	16	—	Fingers, wrists, elbows, knees
7	F 58	3	61	—	" " " "
8	F 40	5	28	—	Fingers, wrists, knees, ankle
9	F 55	12	20	—	Fingers, wrists, knee, ankle
10	F 58	16	47	+	Fingers, wrists, elbows, knees, ankles, feet
11	F 53	6	76	+	Fingers, wrists, shoulders, knees
12	F 50	6	34	—	Fingers, wrists, shoulders, knees, ankles
13	F 45	7	50	—	Fingers, wrists, shoulder, knees, ankles
14	F 58	3	29	—	Fingers, wrists, elbows, knees, ankles
15	F 58	20	38	+	Fingers, wrists, elbows, shoulders, knees
16	F 56	20	58	—	Fingers, wrists, knee, ankles
17	M 43	6	22	—	Knees
18	M 56	5/12	12	—	Wrists, elbows, knee, ankles, feet
19	M 49	4	65	—	Fingers, wrists, elbows, knees
20	M 63	17	20	+	Fingers, wrists, elbows, shoulders, knees
21	M 61	6/12	54	+	Fingers, wrists, knees
22	M 65	4/12	29	—	Fingers, knees
23	M 38	1	30	+	Fingers, wrists, elbows, knees
24	M 60	6	58	—	Fingers, elbows, knees, ankles
25	F 55	22	50	—	Fingers, wrists, knees
26	M 49	8/12	81	—	Fingers, wrist, elbows, knees
27	M 56	3	74	+	Fingers, wrists, elbows, knee, ankles

The following routine investigations were negative in all 27 cases: the blood Wassermann, the gonococcal flocculation test, and the *Brucella abortus* agglutination. The blood uric acid was normal in all patients. The Rose-Waaler test was not carried out routinely.

In one of the poor results—that in a patient with long-standing rheumatoid disease and bilateral effusions—we were unable to space out injections beyond 10-day intervals without recurrence of swelling. Nevertheless

the patient, an ironmongery manager aged 38, who had previously been bedridden, has been able to carry on his business during the past eight months.

The Chart records the number of injections required to produce complete relief of pain and resolution of swelling in these patients.



Number of injections required to produce complete relief of pain and resolution of swelling in 44 rheumatoid joints.

Osteoarthritis

The number of cases in this and the succeeding group are too small to permit detailed analysis. Of the six cases a good result was obtained in two (Cases A and B); a fair result in two (Cases C and D), in that regular maintenance injections have been required; and a poor result in two (Cases E and F).

Case A.—An obese woman aged 64 years had had pain and swelling of both knees for five years. There was moderate effusion in both knees and *x*-ray examination showed marked bilateral osteoarthritic lipping. The E.S.R. was 6 mm. in one hour. After treatment the effusions absorbed and she obtained lasting relief of pain.

Case B.—A night sister aged 50 had a five-years history of pain and swelling of both knees. She was obese, and there were moderate effusions in both joints with marked crepitations on movement. The E.S.R. was 6 mm. in one hour. X-ray examination showed marked osteoarthritic changes in both knees and less severe changes in the right hip and lumbar spine. Since treatment she has been able to resume her duties and to enjoy swimming again.

Case C.—Since an injury to her right knee nine years ago this 63-year-old woman had severe pain in the joint, with swelling and instability. Examination disclosed a large effusion and marked crepitus on movement. The E.S.R. was 6 mm. in one hour. *X*-ray examination showed gross osteoarthritic lipping and loss of joint space. After treatment the effusion cleared, but she needed injections at 10-day intervals to keep her free of pain.

Case D.—A 47-year-old woman had a history of pain and swelling of the right knee for 11 years. There was a moderate effusion into the joint. The E.S.R. was 12 mm. in one hour. *X*-ray examination showed an old healed fracture in the lower half of the right femur with deformity, and there was gross osteoarthritis of the right knee-joint. After treatment there was relief of pain and increased joint movement, but unless injected at fortnightly intervals she tended to relapse. She is, however, able to continue working as a printer's assistant.

Case E.—An obese woman aged 56 complained of pain and swelling of both knees of seven years' duration. The E.S.R. was 15 mm. in one hour. There was thickening of the joints, with crepitations on movement. *X*-ray examination showed marked osteoarthritic changes in both knees with considerable diminution of joint space. Treatment produced no notable change.

Case F.—An obese woman of 52 had had osteoarthritis of the left knee for seven years. On examination there was a large effusion with crepitus on movement and marked muscle-wasting. The E.S.R. was 8 mm. in one hour. *X*-ray examination showed osteoarthritic lipping and diminution of joint space. The effusion cleared after a course of injections, but she did not obtain significant symptomatic benefit.

Recurrent Hydrarthrosis

In both of the following cases the results of treatment were good.

Case I.—A bookbinder aged 32 had had painless swelling of both knees for three years. Investigations, including synovial biopsy, serological examination, and repeated culture of the joint fluid, had shown no specific disease. The swelling resolved after four injections in one knee and eight in the other, and there has been no recurrence during the six-months period of follow-up.

Case II.—A housewife aged 36 had had persistent swelling of both knees for one year. The swelling completely resolved in one knee after three injections and in the other after four injections. There has been no recurrence during the nine-months period of follow-up.

Control Group

Ten patients with bilateral effusions of comparable severity were selected. One knee was used initially as a control. A similar procedure was carried out in both knees, one receiving prednisolone trimethylacetate and the other an equal volume of lignocaine, the patient and one of us being unaware which side was chosen. The control knees received two injections of lignocaine at weekly intervals with the exception of three cases where the marked contrast in pain between the knees after the first injection made it unjustifiable to continue the experiment. When at the end of the control period the active drug was given to the joints having lignocaine, resolution of pain and swelling occurred in all. These results are summarized in Table III.

TABLE III.—*Response of Pain and Swelling to Injection in Control and Treated Groups at End of Control Period*

Degree of Improvement	Pain		Swelling	
	Treated*	Control	Treated	Control
Nil	—	7	—	9
Slight	—	1	3	1
Moderate	4	1	7	—
Marked	5	1	—	—

* One case was painless throughout.

Discussion

The variable results obtained with hydrocortisone acetate may be due to the rapidity with which the compound is absorbed into the circulation. Wilson *et al.* (1955) showed that after an injection of hydrocortisone acetate 86% of the drug had disappeared from the joint at the end of one hour, and 97% at the end of three hours. Thirty minutes after injection, appreciable amounts of what was probably hydrocortisone were found in the uninjected contralateral knee. The findings of Oka (1956) are in general agreement. The plasma 17-hydroxycorticosteroid levels after intra-articular injection of hydrocortisone were found to be so high that systemic hormonal effects were to be expected if large and frequent doses were used. Oral or intra-articular hydrocortisone acetate gave peak blood levels three hours after administration.

Attempts have been made to find a longer-acting steroid compound. Hollander *et al.* (1954) undertook

clinical trials of a number of compounds, including 9 - alpha - chlorohydrocortisone, allo - dihydrohydro - cortisone, and two higher esters—hydrocortisone caprylate and hydrocortisone benzoate. While benefit was obtained in a few cases by one or the other, it was noted that the 9-alpha-chlorohydrocortisone compound could cause fluid retention. The hydrocortisone benzoate preparation gave rise to synovial irritation. None of the compounds gave such consistent improvement as hydrocortisone tertiary butyl-acetate. Duff *et al.* (1955) found hydrocortisone tertiary butyl-acetate more effective than hydrocortisone acetate in 50% of cases. Rothermich and Philips (1957) considered hydrocortisone tertiary butyl-acetate the more effective of the two. In a further paper, Hollander *et al.* (1955) found the tertiary butyl-acetate to give a longer and more complete response in 60% of cases than was obtained with hydrocortisone acetate. Nevertheless in 35% no advantage was noted and in 5% hydrocortisone acetate gave a better result. Freyberg's (1954) findings were less encouraging, since only 39% of his patients responded for a significantly longer period. Zickner *et al.* (1956), however, found that there was no significant difference between hydrocortisone and hydrocortisone tertiary butyl-acetate in degree or duration of improvement.

There are few reports of prednisolone trimethyl-acetate in the literature, and none containing controls. Thompson (1957) reported no significant difference between prednisolone acetate, prednisolone trimethyl-acetate, and hydrocortisone acetate in the treatment of large or medium-sized rheumatoid joints. Glyn and Newton (1958) comment that limited experience has not shown prednisolone trimethylacetate to possess any advantage over hydrocortisone acetate. They were, however, referring to the treatment of soft-tissue lesions.

In chronic disease it is often difficult to evaluate a new therapeutic substance because of the psychological response of the patient to a different form of therapy. In discussing their results of intra-articular injections—to the patient a dramatic form of treatment—few authors appear to have taken this into consideration. Fearnley *et al.* (1956), in a controlled cross-over trial using hydrocortisone acetate or 2% procaine fortnightly for four injections, showed that the only significant difference was that found between the results of the first treatment and that of the second, regardless of which drug was used. Leveaux and Quin (1956) in osteoarthritis of the hip compared procaine with hydrocortisone and procaine in two comparable groups. The results of the first injection in each group were remarkably similar. The results of the second showed the superiority of hydrocortisone. This difference could not be explained on an organic basis. The authors emphasized the influence of psychological factors on the response to first injections.

The results of our control experiment differ from the above in that the active compound was shown to be superior from the start, but we assessed the control and active compounds simultaneously in each patient. This may partly explain the difference. It is also possible that we were dealing with a more potent drug.

It seems likely that the action of prednisolone trimethylacetate is a local one. There was no evidence of general systemic effect on our patients. In particular, the sedimentation rates showed no significant change. There was no improvement in joints other than those injected, and this is well demonstrated by the control group. During treatment there was evidence of fresh activity in other joints in eight patients, whereas improvement in the knees continued.

Our experience over a period of 14 months in the treatment and follow-up study of the patients reported has shown that prednisolone trimethylacetate is an effective agent for intra-articular therapy. In addition, the superiority of the cytological and biochemical changes in the joint fluid produced by the drug (Murdoch and Will, 1959), when compared with those published for hydrocortisone, confirms our view, and merits further study.

Summary

A trial of prednisolone trimethylacetate, a new compound for intra-articular therapy, is described.

57 joints were treated in 35 patients. Of those patients, 27 (44 joints) had active rheumatoid arthritis, 6 (9 joints) had osteoarthritis, and 2 (4 joints) had recurrent hydrarthrosis.

In the rheumatoid arthritis group results were good in 23 (85.2%), fair in 2 (7.4%), and poor in 2 (7.4%). Of the six cases of osteoarthritis a good result was obtained in two, a fair result in two, and a poor result in two. In both cases of hydrarthrosis the results of treatment were good. In 10 patients with bilateral effusions, one knee was used initially as a control, being given an equal quantity of lignocaine.

The results obtained over a period of 14 months show that prednisolone trimethylacetate is an effective agent for intra-articular therapy. It would appear to compare favourably with the reported figures for hydrocortisone. The significance of these findings is discussed.

We thank Dr. J. W. Macfarlane for his continued interest and encouragement, and Dr. J. P. Currie who kindly referred patients to us. Dr. C. D. Falconer, medical director, Ciba Laboratories, made a generous supply of prednisolone trimethylacetate ("ultracortenol") available. Finally this trial would not have been possible without the willing co-operation of the sisters in wards 10 and 11, Glasgow Royal Infirmary, and ward B4, Eastern District Hospital.

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