The condition was suspected clinically and diagnosed pre-operatively by cardiac catheterization and retrograde angiocardigraphy.

The abnormally large left circumflex coronary artery entered the coronary sinus.

Surgical ligation of the coronary artery has resulted in noticeable improvement in the patient's cardiovascular status.

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METHYLPREDNISOLONE ACETATE IN INTRA-ARTICULAR THERAPY

CLINICAL, BIOCHEMICAL, AND CHROMATOGRAPHIC STUDIES

BY

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In rheumatoid arthritis the local and general symptoms are often adequately controlled by physiotherapy combined with analgesics or oral steroids. Yet in some patients, while there is general improvement with this treatment, acute symptoms persist in one or more joints. This is particularly so in the weight-bearing joints, where pain and effusion may severely limit mobility. In such cases intra-articular therapy would appear to have much to commend it, as it should be possible to ensure a high local concentration of steroid while avoiding the side-effects of systemic administration.

In recent years a number of synthetic steroids of greater potency than the original compounds—cortisone and hydrocortisone—have been produced. Some of these compounds are suitable for intra-articular injection. We report here our experience with the intra-articular administration of a new steroid, methylprednisolone acetate.

The Investigation

As in our previous work (Murdoch and Will, 1959a), knee-joints were used, their size and ease of access making it possible to obtain serial specimens of joint fluid. Joint effusion was tabulated into four grades: marked (+++); moderate (++); slight, where there was patellar tap only (+); and no effusion. Pain was assessed in four grades: severe (+++); moderate (++), mild (+), and absent. The cytological and biochemical changes of the joint fluid were studied, and an assessment was made of the persistence of the steroid within the joint cavity. During the trial a standard dose of 40 mg. of methylprednisolone acetate in 1 ml. was injected at weekly intervals until complete relief of pain and swelling was obtained.

Aspirations were carried out in 69 joints. The total number of rheumatoid patients was 48. Twenty-six patients were admitted to the wards for the initial period of treatment and were subsequently seen at regular intervals as out-patients. During the period of investigation the patients received no treatment other than simple analgesics.

The knee-joints were entered from the lateral aspect at the level of the upper border of the patella with the limb in extension. Only a small volume of fluid (3–5 ml.) sufficient to permit routine analysis was removed. The number of injections given per joint varied from one to six, with an average of 2.8. The period of follow-up ranged from 10 to 30 months, with an average of 18 months.

In six patients with bilateral effusions of comparable severity one knee was used initially as a control, being given an injection of 1 ml. of lignocaine, while the other knee received the standard dose of methylprednisolone acetate. Thereafter both knees were given the steroid. In contradistinction to the treated knees, the control knees showed no improvement in pain and swelling. The cell count rose in every case, and there was no significant alteration in the protein content. As these results corresponded closely with our previous experience (Murdoch and Will, 1959a, 1959b) the control group was not extended further.

Clinical Results

The initial status of the joints with regard to pain and effusion is shown in Table I. The usual response to injection was relief of pain beginning within six hours and becoming complete within 24 hours. In more than half the patients only two injections were required to produce resolution of the effusion. Where effusions were bilateral the two joints always responded similarly to treatment. Fig. 1 records the number of injections required to produce relief of pain and resolution of

TABLE I.—Initial Status of 69 Joints with Regard to Pain and Effusion

Grade:	+++	++	+	0
Effusion	25	33	11	—
Pain	40	17	11	1

FIG. 1.—Number of injections required to produce complete relief of pain and resolution of effusion in 69 rheumatoid joints. (One joint was painless throughout.)

effusion in these patients. No patient failed to obtain rapid initial relief of pain and effusion. At the end of the follow-up period 49 joints were still in remission without further intra-articular therapy. In the remaining 20 joints relapse occurred, further treatment being required. Two joints relapsed within a month, seven in two months, seven in three months, one at five months, and three at six months. Relapse did not appear to be directly related to the number of injections given.

Biochemical and Cytological Changes

Total and differential white-cell counts, electrophoresis, and estimation of the total protein content of the synovial fluid were carried out as previously described (Murdoch and Will, 1959b). In 52 joints satisfactory serial specimens were available. Effusion cleared so rapidly in the remaining joints that suitable specimens could not be obtained.

The synovial fluid in rheumatoid arthritis is watery, pale yellow, and turbid. Fibrin flakes are often present, and clotting occurs on standing. The cell count is high, polymorphonuclears predominating. The initial average white-cell count was 3,200/c.mm., with a range of 1,200 to 16,000/c.mm. At the end of treatment there was a fall in every case, the average count being 320/c.mm., with a range of 100 to 800/c.mm. The results are summarized in Fig. 2. The initial differential counts showed a polymorphonuclear predominance in all but two joints, the average figure being 76.3%. After treatment there was a sharp diminution of polymorphs in all cases, with the appearance of a relative lymphocytosis. Examination of the absolute figures, however, showed a real drop in all three types—namely, polymorphs, lymphocytes, and monocytes. The final average polymorph percentage was 30.

The total protein content of the joint fluid was estimated by a modification of the biuret method (Gornall *et al.*, 1949). During treatment there was a fall in the total protein in 48 joints, with no change in two, and an increase in two. The initial average protein was 4.1 g. (range 2.55 to 7.35 g.), and the final average

figure was 2.69 g. (range 1.0 to 5.2 g.), the average drop being 1.41 g. These results are summarized in Table II. As the true albumin percentage cannot be estimated in joint fluids by salting-out methods (Yielding *et al.*, 1956), we carried out paper electrophoresis of the fluid in 40

TABLE II.—Initial and Final Proteins (g./100 ml.) in 52 Joints

	-2	-2.5	-3	-3.5	-4	-4.5	-5	-5.5	>5.5
Initial ..	—	—	5	11	6	8	4	11	7
Final ..	9	12	21	5	3	1	—	1	—

joints at a pH of 8.6, using a barbitone buffer (Jencks *et al.*, 1955). The average initial albumin was 35.6% (range 12.9 to 54.4%). During treatment 30 joints showed a rise in albumin content, six were unchanged, while four showed a small drop. The final average albumin was 44.7% (range 26.7 to 57.5%). Detailed analysis of the globulin fractions showed a tendency for all fractions to diminish. This was particularly marked in the γ -globulin fraction (see Table III).

TABLE III.—Effect of Treatment on Electrophoretic Pattern in 40 Joints

Protein Fraction	Rise	No Change	Fall
Albumin ..	30	6	4
α_1 globulin ..	8	13	19
α_2 " ..	9	10	21
β " ..	12	10	18
γ " ..	6	9	25

Chromatographic Studies

To determine the persistence of methylprednisolone acetate within the joint cavity, a separate study was carried out in a further 40 joints which were aspirated at intervals after injection. The joints were drained as completely as possible, and were then washed out with 40 to 50 ml. of warm sterile isotonic saline. The steroid was then extracted from the synovial fluid and washings as previously described (Will and Murdoch, 1960). The chromatograms were then run in a descending chromatography tank using the solvent system of Bush (1952). The B5 system (water, methyl alcohol, and benzene) was found to be the most suitable. The steroid present was identified by (1) the absorption of ultra-violet light of wavelength 253 m μ , (2) the reduction of blue tetrazolium reagent (Burton *et al.*, 1951), and (3) the position on the chromatogram in relation to the markers.

Chromatograms were prepared from specimens obtained at intervals of 7 to 21 days after the injection of a standard dose of 40 mg. (1 ml.) of methylprednisolone acetate. Steroid was recovered from three-quarters of the joints examined. These results are summarized in Table IV.

TABLE IV.—Chromatographic Detection of Steroid in Joint Fluid Using a Standard Dose of 40 mg. Methylprednisolone Acetate

Time in days:	7	10	14	21
No. of joints injected	20	7	10	3
No. of synovial fluid specimens containing steroid	15	6	7	2

Discussion

In assessing the suitability of a steroid for intra-articular therapy we feel there are three main criteria which should be fulfilled. The compound used must have a marked local anti-inflammatory action, as shown

FIG. 2.—White-cell count before and after treatment with methylprednisolone acetate in 52 joints.

by relief of pain and swelling of the joint. This symptomatic improvement should be accompanied by a return towards normal of the cellular and biochemical abnormalities within the joint. Lastly, it should be possible to demonstrate the persistence of the steroid locally for a prolonged period.

The compound most often used has been hydrocortisone. While this has a marked local anti-inflammatory action, it produces symptomatic improvement of a temporary nature in no more than 50% of cases (Duff, 1956; Sairanen, 1956). This is accompanied by an inconstant fall in the white-cell count lasting for only a few days (Robinson *et al.*, 1955). There is little or no change in the total protein concentration (Dixon and Bywaters, 1953; Sundblad *et al.*, 1954), nor are there changes in the albumin/globulin ratio (Ziff *et al.*, 1953) or electrophoretic pattern (Jessar *et al.*, 1953). This is perhaps not surprising in view of the findings of Wilson *et al.* (1955) that after the injection of hydrocortisone acetate 86% of the drug had disappeared from the joint at the end of an hour, and 97% at the end of three hours. The findings of Oka (1956) are in agreement. We found that even after the intra-articular administration of 150 mg. of hydrocortisone acetate, steroid could not be demonstrated in the joint cavity 24 hours later (Will and Murdoch, 1960).

It is recognized that methylprednisolone has a local anti-inflammatory effect at least equivalent to that of prednisolone, if not more potent (Neustadt, 1958; Kleeman *et al.*, 1958). Our studies show that methylprednisolone acetate produces symptomatic relief of satisfactory duration in a high proportion of patients. This is accompanied by a progressive improvement in the cellular and biochemical abnormalities of the fluid. We have been able to recover steroid from the joints up to 21 days after injection. The drug would thus seem to satisfy all our criteria.

The evidence of local persistence of steroid provided by our chromatographic studies has led us, as with other workers (Norcross, 1958; Cardoe, 1959), to use a larger standard dose for intra-articular therapy, with consequently a shorter course of injections. It is therefore not possible to make a direct comparison with our previous work on prednisolone trimethylacetate (Murdoch and Will, 1959a, 1959b). However, allowing for the different dosage schedules, almost similar results are obtained. While methylprednisolone acetate produced more rapid resolutions of effusion, pain was more effectively controlled by prednisolone trimethylacetate. There was little difference in the cytological, biochemical, and electrophoretic findings. Chromatographic studies of the persistence of the steroid favour methylprednisolone acetate, but this compound had a higher relapse rate.

Chandler *et al.* (1958, 1959) have shown that progressive joint deterioration may occur after repeated injections of hydrocortisone preparations, and suggest that radiological control is desirable. One of their osteoarthritic patients developed changes resembling a Charcot arthropathy. During our present study we have not encountered such changes. This may be due in part to the use of a more potent compound, and in consequence fewer injections.

Where intra-articular therapy is indicated we suggest that methylprednisolone acetate, or a similar long-acting steroid, be used in preference to hydrocortisone.

Summary

Methylprednisolone acetate, a new compound for intra-articular injection, was given to 48 patients with rheumatoid arthritis. There was initial relief of pain and effusion in all 69 joints treated. At the end of the follow-up period, 49 joints were still in remission. The cytological and biochemical changes in the joint fluid were studied. Using chromatographic techniques the drug was shown to persist in the joint cavity for as long as 21 days.

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The main section of the *Annual Report of the Advisory Council on Scientific Policy for 1960-1961* deals with the problems of the organization of scientific research, in particular the provision and use of costly research equipment. The Council have not yet formulated a final view on these questions, which will require further consideration. The opening section comments on the recently published report of the Council's Scientific Manpower Committee on the "Long-Term Demand for Scientific Manpower" (Cmd. 1490). The Council notes that this report has been seriously misunderstood in some quarters, and has been described as conflicting with previous predictions of a shortage of scientific manpower. The Council comments that the prospect that the shortage may be easing is due to a succession of Government plans to increase the scale of higher scientific and technical education, which have been developed largely on the basis of past advice by the Manpower Committee. Already the number of new qualifications annually stands at nearly 17,000, or three times the pre-war level, while, if all goes according to plans now under way, there will be a six-times increase by early in the 1970s. The Manpower Committee is considering how workers with medical, dental, agricultural, or veterinary qualifications might be included in the three-yearly review which will be undertaken in 1962. (H.M.S.O., price 1s. 6d. net.)