TWO YEARS' EXPERIENCE OF PREDNISONE IN RHEUMATOID ARTHRITIS*

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Early in 1955 Bunim and his colleagues reported on the use of two analogues of cortisone, prednisone ("metacortandracin") and prednisolone ("metacortandralone"), in the treatment of rheumatoid arthritis. These two steroids differ from cortisone and hydrocortisone respectively in possessing a double bond between carbon atoms 1 and 2 of the A ring of the molecule. This small structural change is responsible for two notable differences between parent and offspring; the latter are weight for weight three to four times as potent as cortisone, and they do not cause sodium retention in therapeutic dosage. There is little to choose in action between prednisone and prednisolone; in general their effects are the same as those of cortisone, except that they have gained in some quarters a particular reputation for promoting dyspepsia, peptic ulceration, and haemorrhage.

In 1955 both steroids became available for hospital use and later were released for prescription on form E.C.10. The situation has thus arisen that two powerful drugs, about which comparatively little has been published in this country, are widely available. In this instance a volume of advertising has eclipsed the literature, and both steroids can be obtained not only as such but in compound form, either with an antacid or in small amount in combination with aspirin. Satisfactory proof is lacking that the first confers safety or that the second is efficacious. We here record our experience with one of these steroids, prednisone, over a two-year period. It must be emphasized that what follows is a retrospective analysis of the practice of a rheumatism clinic, and not a report of an organized clinical trial designed in advance and statistically controlled.

The Patients

From June 15, 1955, to June 15, 1957, in a new rheumatism clinic, a total of 167 patients with rheumatoid arthritis were seen. Many of these patients in the past had received gold, phenylbutazone, cortisone, and corticotrophin; most had received simple analgesics of aspirin type; none to our knowledge had been given either prednisone or prednisolone. The practice of the clinic was to assess each patient when seen, or after any necessary investigations, in regard to activity, extent and severity, and interference with function. Patient with mild arthritis and little limitation of function are advised about rest and exercise, the value of aspirin, and simple self-administered physiotherapy. They are referred back to the care of their own doctors, but usually asked to attend the clinic for review at six-monthly or yearly intervals. Patients with moderately severe disease attend the clinic regularly and are given interrupted courses

of physiotherapy, splintage, local hydrocortisone where applicable, and simple orthopaedic appliances when indicated. Severe cases fall into the following categories: (1) those with severe acute arthritis, often of recent onset; whenever possible such patients are admitted for in-patient treatment; (2) patients who have recently become bed-fast or chair-fast; again some but not all of these require admission; and (3) patients whose capacity for work is becoming impaired. Obviously these groups are not distinct; there is much overlap. Nearly all patients in groups 2 and 3 have had a prolonged trial of aspirin type of analgesic in adequate dosage, and many have had a variety of other drugs as well. The patients in these two groups present a therapeutic challenge, and neither they nor very often their doctors are always comforted by an assurance that they will do as well on aspirin as anything else. Our policy with regard to groups 2 and 3 has been to treat each patient according to his or her merits, but to restrict drug therapy whenever possible to the aspirin group for a period of time at least. Latterly we find that, with increasing experience of prednisone, we tend to use it rather earlier than we did initially and that the criteria for its administration have become less stringent.

Drugs Used

Table I shows the drugs used in the treatment of 167 patients with rheumatoid arthritis, together with the transfers from one drug to another. It has been possible to maintain the majority (105) on aspirin. The 15 patients started

TABLE I.—*Drugs Used in 167 Cases of Rheumatoid Arthritis*

Drugs Used	Initially	Finally
Aspirin	129	105
Phenylbutazone	15	15
Cortisone	8	0
Prednisone	15	47

Transfers			
Aspirin	to prednisone ..	..	16
"	" cortisone ..	..	1
"	" phenylbutazone ..	..	9
Phenylbutazone	" aspirin ..	..	1
"	" prednisone ..	..	8
Cortisone	" aspirin ..	..	1
"	" prednisone ..	..	8

on phenylbutazone are not identical with the 15 patients having phenylbutazone at the final assessment because of transfers between groups. Cortisone was used initially in only eight patients, and only one patient was transferred from aspirin to cortisone, and later back to aspirin. The reason for this is that quite early in the two-year period the results obtained with prednisone appeared better than those obtained with cortisone, and we have for some time stopped using the latter. Fifteen patients were started on prednisone when first seen, but by June, 1957, the number receiving this steroid had risen to 47, the increase being accounted for by transfers from the other groups. It will be noted that all eight patients started on cortisone were eventually changed to prednisone.

In addition to the 47 patients who had been started on prednisone by June, 1957, there were two who moved to another neighbourhood, and, being unavailable for assessment, are not included. In three patients of the prednisone group the drug was discontinued; in two, a man and woman, because of spontaneous remission at six and eight months after prednisone was started, and in one, a woman, because of severe hypertension at five and a half months. The arthritis of this patient has also gone into remission, but the hypertension persists and has recently been complicated by subarachnoid haemorrhage. Unfortunately this patient is one of the few who did not have a blood-pressure reading taken at the start of steroid therapy, the hypertension being discovered two months later. The remaining patients, 44 in number, are still receiving prednisone. The Chart overleaf shows the age and duration of disease of the prednisone-treated patients; the greater number are in the older age groups.

*Based on the opening paper in a symposium on steroid therapy in rheumatic diseases at the meeting of the Section of Physical Medicine at the Annual Meeting of the British Medical Association, Newcastle upon Tyne, 1957.

The initial dose of prednisone was 5 mg. eight-hourly, and in only one patient has the dose been increased to 20 mg. daily. In eight patients the dose was reduced to 2.5 mg. eight-hourly, but the remainder have not tolerated reduction and are maintained on the 5-mg. dose. Recently we started

Age of patients on prednisone and duration of their rheumatoid arthritis.

to use an initial dose of 2.5 mg. eight-hourly, but this does not apply to the patients in this series. Patients on steroid therapy were for the most part seen monthly at the clinic. Latterly those well under control and devoid of complications were seen at intervals of two months. At each attendance inquiry was made about dyspepsia in particular, and a routine blood pressure, urine, and weight check carried out. We have not found it necessary to determine serum electrolytes. A barium-meal examination was done in any patient who developed anything more than mild transient dyspepsia.

Complications

Table II shows the complications encountered in relation to duration of prednisone therapy. Dyspepsia was fairly common, in line with the experience of others, occurring in

TABLE II.—Complications During Prednisone Treatment of 47 Patients

Months of Therapy:	0-		6-		12-		18-24		Totals
	F	M	F	M	F	M	F	M	
No. of patients ..	5	6	10	7	9	3	6	1	
Dyspepsia ..			1	1	1		1		4
X-ray-negative dyspepsia ..	1		2	1	1				5
Peptic ulcer ..					1		1		2
Obesity ..				1	2		1		4
Hypertension ..					1		1		2
Diabetes ..				1					1
Other ..			1				1		2

11 patients. In four patients the dyspepsia was mild and transient; in five it was persistent, requiring an antacid for its control, but the barium-meal examination has so far been negative. These patients are being closely observed, but all of them appear to be free of epigastric pain provided that a dose of antacid is taken with each dose of prednisone. They regard this as a minor price for the improvement in their arthritis, but we are unable to feel complacent, since we do not believe that control of symptoms in this way necessarily confers safety. For this reason we reject the use of tablets containing prednisone together with an antacid, certainly when used routinely from the outset, since nobody has proved that epigastric pain after taking prednisone is not a pointer to the risk of perforation or haemorrhage, and to mask such a pointer seems indefensible. But we also prefer to give a separate antacid to patients who have developed

epigastric pain on prednisone, since this serves to remind doctor and patient that all is not as well as it should be. Two patients have developed peptic ulcers. In one, whose barium-meal examination showed an active duodenal ulcer, prednisone was gradually withdrawn, with resulting relapse of the arthritis. The other patient whose barium meal showed a prepyloric ulcer is being maintained on prednisone and an ulcer regime in response to her entreaties. A recent barium-meal examination no longer showed an ulcer crater.

Although dyspepsia was the commonest complication, its incidence in these patients (23%) was less than that in the 24 patients given phenylbutazone, of whom 11 developed dyspepsia, an incidence of 46%.

Of the remaining complications, obesity has not been a problem; it was pronounced in four patients and is now controlled by diet in three of them. A few patients developed mooning of the faces, and two had a mild acneiform eruption. The blood pressure was raised in two patients. In one, mentioned previously, it cannot be definitely ascribed to steroid therapy; in the second, a middle-aged woman, the blood pressure rose from 140/80 to 190/100 since she had prednisone, but this is not considered sufficient to withdraw the drug.

Diabetes occurred in one case, an account of which is given below. Another patient, a middle-aged woman, already a diabetic, requires increased insulin while on prednisone. One patient, a woman with a past history of "nervous breakdown," in spite of great improvement of her arthritis became agitated and depressed and the drug has recently been withdrawn. Another patient, a woman, developed a syndrome of agitation, tiredness, and generalized weakness, all of which have subsided on continued prednisone.

Results

In a busy rheumatism clinic it is not always possible to make as many observations as are desirable. For this reason some of the currently used criteria—for example hand grip, joint tenderness, range of joint movement, and E.S.R. were not used routinely. When first seen each patient with rheumatoid arthritis was fully examined, and their joint status assessed in regard to the joints involved, also their range of movement and function. The patients' functional status was recorded in the conventional five grades, as follows. Grade 1, confined to bed; grade 2, bed or chair existence with limited mobility indoors; grade 3, able to get about but capable of only limited housework—unfit for employment; grade 4, capable of light work; grade 5, fully active. Particular note was taken of the patients' background and responsibilities and their capacity to fulfil the latter. At the time of analysis, therefore, it was possible to contrast the patients' status and function in relation to their responsibilities and social activities to that which obtained when they were first seen. From the patients' point of view we believe that successful treatment means, firstly, diminution of discomfort, and, secondly, which in part is consequent upon the first, the capacity for work and the capacity for enjoyment. "I can now look after my garden, which I could not do before" may be to the patient a therapeutic triumph.

Table III shows the functional status of 47 patients treated with prednisone when first seen and at the time of final assessment. It can be seen that there has been a shift to

TABLE III.—Functional Status of 47 Patients Treated with Prednisone

Functional Status	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Initial	3	9	22	12	1
Final	0	4	17	18	8

the right, there being finally no patients in grade 1, eight patients in grade 5, as opposed to 1 initially, an increase of the number in grade 4, and a decrease of the number in grade 3. Table IV shows the change in functional status related to the duration of therapy. Only one patient, a

woman, deteriorated in functional status; 16 of 30 women and 9 of 17 men improved; in the remainder functional status was unchanged.

TABLE IV.—*Change of Functional Status*

Months of Therapy:	0–		6–		12–		18–24		Total	
No. of Patients:	F 5	M 6	F 10	M 7	F 9	M 3	F 6	M 1	F 30	M 17
Change of status:										
–2			1						1	0
–1									0	0
0	2	3	2	3	5	2	4		13	8
1	2	2	7	2	4		2	1	15	5
2		1		1						2
3	1								1	1
4						1				1
Mean change	1.0	0.7	0.5	1.0	0.4	1.3	0.3	1.0	0.5	0.9

Figures in the left-hand column refer to change of status and not actual status.

Table V shows the patients' own assessment of their improvement or otherwise since treatment with prednisone. Two patients in their own estimation had deteriorated badly

TABLE V.—*Subjective Improvement*

Months of Therapy:	0–		6–		12–		18–24		Total	
No. of Patients:	F 5	M 6	F 10	M 7	F 9	M 3	F 6	M 1	F 30	M 17
Very much worse ..			1	1					1	1
Somewhat worse ..									0	0
No change ..		1			1				1	1
Somewhat better ..		1	1	1	2	1			3	3
Very much better ..	5	4	8	5	6	2	6	1	25	12
Mean change	2.0	1.5	1.5	1.3	1.5	1.7	2.0	2.0	1.8	1.5

(one of these was the patient whose functional status had dropped two points; the functional status of the other had remained unchanged). Two patients reported no improvement, six reported only moderate improvement, 37 reported marked improvement. In all, 43 patients believed themselves to have improved since treatment with prednisone. This is greater than the "inevitable 60%" expected to improve whatever the therapy.

Although others have found it necessary to increase the dosage after a period to combat return of symptoms (Black *et al.*, 1955), so far we have not had occasion to do so. We do not subscribe to the popular practice of starting with a large dose and tapering down to a smaller maintenance dose, because some of the dramatic initial improvement may be lost as the dose is reduced in the presence of massive depression of the patients' own adrenals. It seems more logical to begin with a small dose and increase it if necessary.

The following case histories illustrate two very different problems in which prednisone has been helpful.

Case A.—A man of 35 had rheumatoid arthritis of six months' duration involving the whole of the right hand and wrist. No other joints were involved, but in the presence of a useless left arm and hand resulting from Erb's palsy he was quite unable to work as a clerk. Large doses of aspirin, wax baths, and a night splint were first tried without effect. He was then given phenylbutazone without improvement. After two weeks on prednisone, 5 mg. thrice daily, his right hand was virtually normal and he returned to work.

Case B.—A retired Army officer aged 64, when first seen in October, 1955, could barely get about the house with the aid of crutches. He was in constant pain or discomfort and his morale was very low. Although the rheumatoid arthritis was generalized, with characteristic deformities of the upper limbs, his greatest sources of pain and disability were his knee-joints, both of which were in flexion deformity with about 50% limitation of movement. Passive movement revealed the coarse creaking one associates with gross cartilage destruction. He was admitted and

advised to have an arthrodesis on one knee, but this he steadfastly refused in the hope that "some new treatment might come along." For a time, and rather unexpectedly, both knees improved on hydrocortisone injections every fortnight, and he was able to get about painlessly on his crutches. Gradually, however, the injections became less effective and at the end of a year he experienced relief for only two or three days after the injection. A past history of peptic ulcer and severe haematemesis had hitherto forbidden systemic steroid therapy. However, after a "hydrocortisone holiday" of nine months he reverted to his previous state, brightened by two to three days' relief every fortnight. After full discussion with him of the risks involved, he was admitted to hospital in October, 1956, for prednisone therapy. In spite of fears to the contrary, he had had no ulcer symptoms up to the time of writing, was free from pain, got about the village in which he lived, and daily went for a walk of about a mile on his crutches. After being on prednisone for two months he developed diabetes, which required insulin for its control.

To begin with, both in-patients and out-patients with severe disease were given an initial trial of aspirin, whatever their previous treatment. As our experience with prednisone has increased, however, we have tended to use it earlier, often without an initial trial of aspirin in patients who have had adequate aspirin dosage without relief for some time before attending hospital. This applies especially to young women with heavy family responsibilities, and men and women who have recently had to stop work or are on the point of being unable to continue. The demand of these patients for something to be done can be urgent, and, when it is, a detached and philosophical attitude to their disease would be inhumane. Fortunately such patients are a minority: in this series they represent most of the 15 who were started on prednisone when first seen.

Of the 167 patients with rheumatoid arthritis, 15 (about 10%) were deemed to require prednisone initially; but at the end of two years 47 (about 30%) were receiving the drug. This may seem a large percentage, but it must be remembered that most patients are referred to hospital because their disease is severe. The figure should not be taken as applicable to the rheumatoid population as a whole.

Discussion

The enthusiasm for cortisone in the treatment of rheumatoid arthritis which swept America some years ago was fortunately modified in this country by the cold scrutiny of the M.R.C. and E.R.C. cortisone-aspirin trials. It is no criticism of the conclusions of these trials, however, to suggest that, valuable though they were in putting cortisone in a proper perspective, they did not, nor did they attempt to, solve the therapeutic problem of the individual patient. It would be unrealistic to question the validity of the general experience of particular patients who have done badly on aspirin and well on cortisone, who have relapsed when the latter has been reduced or withdrawn and remitted when the drug has been reintroduced. For a time, at any rate, some patients have done well on cortisone, and whether their rheumatoid status turns out to be no better after, say, five years on cortisone than after five years on aspirin is not the only consideration. For this reason we believe that rheumatologists, with a few exceptions, have continued to use cortisone if only as a last resource. The practice of physicians throughout the country is, however, unknown, with the notable exception of Copeman *et al.* (1952, 1954), whose searching reports have been invaluable. Certainly, when the question of steroid therapy comes up at panel discussions, there is an atmosphere of disagreement and uncertainty. It must be admitted, however, that many, though not all, patients who improve on cortisone do not maintain their response; that it is a drug of great hazard is indisputable.

Because cortisone had been welcomed with hope and rejected with disappointment, the advent of prednisone and prednisolone evoked limited enthusiasm. Nabarro *et al.* (1955) feared that their absence of sodium-retaining effect might be a disadvantage in that one of the safeguards against increasing dosage to a really dangerous level would be removed.

After the two-year analysis reported here had been completed the first report of the Joint Committee of the Medical Research Council and the Nuffield Foundation was published (1957). In this carefully controlled trial prednisone comes out rather better than cortisone. In America, Black *et al.* (1955) conclude: "Prednisone has been found to be an effective antirheumatic agent in patients with rheumatoid arthritis whose response to other steroids was unsatisfactory. Its antirheumatic potency still appears to be three to four times that of cortisone or hydrocortisone. The return of rheumatic symptoms after 4 to 20 weeks of maintenance therapy may be controlled by a slight increase in the dosage."

The patients' assessment of their own improvement is often viewed with some scepticism, and the well-recognized response of many patients to a placebo justifies this. At the same time, in the everyday practice of medicine subjective improvement is only too often the sole criterion of successful therapy. The history of the treatment of rheumatoid arthritis is so beset with extravagant claims for dubious remedies that a healthy scepticism is desirable; but, like the tendency it counteracts, it too can be overdone. The conventional grades of functional status do not tell the whole story. We have been especially impressed by the fact that the improvement of some of our patients consists not so much in doing more than they did previously as in doing what they have always had to do more quickly, more comfortably, and more expeditiously. There is unfortunately no easy test for this kind of improvement. Without labouring the point, we believe that a report of subjective improvement supplemented by confirmatory answers to experienced questioning is of value.

Three fundamental questions, we believe, must be applied to any new drug used in rheumatoid arthritis: (1) Does it produce substantial relief in a high proportion of patients? (2) Is such relief maintained, and if so for how long? (3) Does the benefit obtained outweigh the risks and complications? From our experience with prednisone the answer to the first question is yes. In regard to the second, we believe that relief has been satisfactorily maintained in most patients so far, but it must be admitted that this belief depends in part on what our patients tell us, which may be subject to many fallacies. The answer to the third question at present is yes; further experience, however, could well cause revision of this opinion. If it be accepted that the newer steroids will help most patients for a time at least, the physician's problem is to know which patients it is justifiable to subject to the hyperadrenal state, however mild, with the risk of the attendant complications. We believe it justified in the cases of the wage-earner on the point of incapacity, the housewife unable to look after a young family, and the patient who is deteriorating rapidly despite all other measures. Whether steroids should be given to patients with milder disease or less arduous commitments cannot be decided until a great deal more experience throughout the world has been gained, and in fact may not need to be decided if research should produce a better and safer remedy.

Summary

The practice of a rheumatism clinic, relating to the treatment of 167 patients with rheumatoid arthritis seen over a two-year period, is reviewed.

Prednisone in a dosage of 15 mg. daily was given to 15 of these patients when first seen; by the end of two years 47 patients were receiving the drug, the increase being accounted for by the failure of other drugs.

The commonest complication of prednisone therapy has been dyspepsia, which occurred in 11 patients, two of whom developed peptic ulcers.

Improvement of functional status occurred in about 50% of patients given prednisone; subjective improvement was reported by 90%.

The value of, and indications for, prednisone in rheumatoid arthritis are discussed.

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SEA-SNAKE BITE

A SURVEY OF FISHING VILLAGES IN NORTH-WEST MALAYA

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In their vast habitat round the shores of the Indian and western Pacific Oceans sea-snakes abound. As they are all venomous and many are highly poisonous, it is fortunate they are not aggressive. Fishermen handle them daily, but there are few records of their being bitten. However, Smith (1926) maintained that casualties were not infrequent, the paucity of reports being due to the incidents occurring in remote localities. Responsible medical authorities rarely observe such cases.

As part of research on sea-snakes, their bites, and poisoning (Reid, 1956) we planned a survey of fishing villages in north-west Malaya to try to find out the incidence of bites, how victims were bitten, and their fate, together with any information of relevance or interest.

Area Surveyed

Fig. 1 indicates the recorded world habitat of sea-snakes (excepting one species, *Pelamis platurus* (Linn.), which extends to western America and eastern Africa). Inset is Malaya. In Fig. 2 the 17 villages visited are shown. They constitute most of the fishing communities of Penang Island and the adjoining 80 miles of coastline of the States of Kedah and Perlis. It was impracticable to include three small villages and the city of George Town, as fishing folk there are too scattered.

TABLE I.—Numbers of Sea-snake Bites per Village with Approximate Populations

Name of Village	Approximate Population	No. of Visits	No. of Sea-snake Bites			
			Fatal	Severe	Trivial	Total
1. Telok Bahang ..	2,000	3	2	—	—	2
2. Tanjung Bungah ..	2,500	2	2	4	4	10
3. Tanjung Tokong ..	5,000	2	2	1	2	5
4. Batu Maung ..	600	4	—	1	3	4
5. Damar Laut ..	1,100	2	—	2	—	2
6. Telok Kumbar ..	3,200	10	4	6	9	19
7. Gertak Sanggul ..	700	2	—	2	2	4
8. Pulau Betong ..	500	3	—	—	2	2
9. Jalan Bahru ..	800	4	3	4	7	14
10. Sungei Pinang ..	1,700	2	—	7	2	9
11. Panteh Acheh ..	800	2	2	3	2	7
12. Kuala Muda ..	3,000	6	11	5	4	20
13. Tanjung Dawai ..	1,700	2	2	—	1	3
14. Sungei Yen ..	4,200	2	2	3	—	5
15. Kuala Kedah ..	7,300	3	6	5	6	17
16. Sanglang ..	1,800	1	3	2	6	11
17. Kuala Perlis ..	3,200	3	2	3	5	10
	40,100	53	41	48	55	144