involvement, and a whole host of rather rare arthritic conditions, some of which are still not fully characterized. There does appear to be a much bigger diagnostic problem than was apparent some years ago, and this may be important both as regards treatment and prognosis.

II

The Management of Rheumatoid Arthritis

J. J. R. Duthie, M.B., CH.B., F.R.C.P. (*Edinburgh*)

Rheumatoid arthritis can be briefly defined as a chronic inflammatory polyarthritis affecting mainly the peripheral joints, running a prolonged, fluctuating course, accompanied by signs of general systemic disturbance, and rather unpredictable. Females are affected two or three times as commonly as males, at least clinically, and the mean age at onset is around 40, though no age is immune.

As regards incidence, according to Dr Lawrence's figures the minimal prevalence of this disease in people over 15 is about 2.1 per cent in males and 5.2 per cent in females, the prevalence rising with age in both sexes. Dr Lawrence states that studies in some seven areas in northern Europe have not produced any evidence of striking difference in regional incidence. On this basis it can be estimated that there are approximately 1,740,000 people in Great Britain over 15 years of age who may be suffering from rheumatoid arthritis of a definite or probable type. I think we must all agree that this constitutes a very formidable problem, particularly so when we must admit that it is a disease of unknown aetiology, running a variable and largely unpredictable course, for which we have as yet no satifactory cure but which is best controlled by a regimen of treatment involving a period of rest in bed under skilled supervision, followed by a carefully graduated course of remedial activity and prolonged and assiduous after-care.

It can be readily seen that in any service for the diagnosis and treatment of the chronic rheumatic diseases, rheumatoid arthritis will make heavy demands on both time and facilities. My own experience over the last ten years amply confirms this view. An

analysis of the patients referred to our unit in Edinburgh between 1950 and 1960 showed that of a total of 6,556 cases a diagnosis of arthritis of the rheumatoid type was made in 2,076, constituting 31.6 per cent of all the cases referred to the unit. The other large groups are osteoarthritis, 30.7 per cent and the heterogeneous group of non-articular rheumatism, perhaps better called pain of undifferentiated origin, 22.1 per cent. What demands do these patients with rheumatoid arthritis make upon hospital accommodation? In Edinburgh we have 30 beds, 15 male and 15 female, and out of a total of 2,003 cases of adult rheumatoid arthritis seen during the 10-year period under review, 733 patients were admitted within one year of the first consultation and 163 later on. This is a total of 896 patients, constituting 45 per cent of all the cases of rheumatoid arthritis seen; in other words, just under half, in our opinion at least, were in need of a period of inpatient treatment. During 1960, 759 new patients were referred to the unit for consultation, of whom 190 had rheumatoid arthritis, that is, 25 per cent of all the patients seen. A total of 202 patients were admitted to the wards of the unit during this year; 91 with rheumatoid arthritis were admitted for the first time, and 65 were readmitted because of an exacerbation of symptoms. Thus of the 202 patients admitted during 1960, 156 were suffering from rheumatoid arthritis, which is 77 per cent of all admissions.

During the last ten years, claims have been made on behalf of a formidable number of new and potentially toxic drugs for treatment of rheumatoid arthritis. In the early stages of the clinic at Edinburgh, I felt very strongly that in order to assess the value of any of these new methods of treatment, a much more detailed knowledge of the course and prognosis in patients treated along conservative lines was essential. For this purpose we have followed the course of some 300 patients admitted to the unit between 1948 and 1951. All were considered in need of hospital treatment because of increasing disability, signs of active disease, presence of deformities, or a combination of all three. In this sense they were a selected group representing the more serious forms of the disease. While in hospital the basic regimen of treatment was a period of rest in bed, the application of plaster-of-paris splints to the affected joint, maximum tolerable doses of that wonderful drug aspirin, daily simple physiotherapy and maintenance exercises designed to prevent unnecessary deterioration in the overall physical condition during this period of initial bed rest. This was followed by a graduated resumption of weight-bearing until an optimal functional level had been attained, and I agree with what has been said about taking patients into your confidence at this stage. If you set your sights too

high, nothing but disappointment will follow both for the patient and yourself. You have got to talk the patient into living with this disease, and the opportunity arising in hospital can be put to good use. For some unstable joints, such as the knee, some more permanent form of support was provided.

I would like to add a few remarks on basic features of treatment. Many of us order patients to bed as part of treatment and do not really think about what this entails in the normal anatomical alignment of the patient. Someone covered with blankets and cages may look perfectly comfortable, but in fact the long spinal muscles may be on the stretch, the knees flexed, the abdominal muscles relaxed, the chest in the position of expiration and the feet unsupported. This neglect of simple elementary attention to postural alightment is really what has made bed rest in rheumatoid arthritis open to very grave criticism. A bed cage should not just be thrown over the patient and left to be pushed away but fitted with a proper footrest and anchored to the side of the bed so that the feet are well supported. A properly arranged back-rest with the minimum number of pillows keeps the spine in good alignment. We are great believers in putting prophylactic splints on joints, even though no deformity has as yet developed.

As regards exercise, again I think we forget that when someone is put to bed, large muscle masses (the gluteal muscles, lumbar muscles, abdominal muscles) are all put out of action; as you know disuse leads to weakness and wasting, and you really are creating unnecessary difficulties in subsequent rehabilitation if you allow this unnecessary deterioration of physical function. Maintenance exercises are done under supervision by the physiotherapist, who is quite clear as to their objective. She is not exercising muscles in relationship to damaged joints, but is aiming at a modest stimulation of cardiac and respiratory function to keep the patient reasonably fit. There is nobody too old or too crippled to do at least a proportion of these general maintenance exercises, and I am perfectly sure that everybody forced to stay in bed for a long time who is not acutely ill and febrile or has a coronary thrombosis would be very much the better for some simple treatment of this kind. Once the signs of inflammation have subsided, there is only one way of really building muscle, and that is to use graduated exercise, increasing the load on the muscle as function improves. A great deal of misdirected physical treatment is given where this principle is ignored—though not so much nowadays, I think. At one time a patient would go on doing the same exercise, day in, day out, week in, week out, which was quite beneficial to start with but had later become quite ineffective. Exercises need not be done in the physiotherapy department; a pulley can be fitted to the patient's bed with a set of graduated

weights. You can apply this principle to any of the joints in the body by arranging the patient in proper relationship to a single pulley. When deformity has occurred before we see these people (fortunately in our area this is getting a little less common, as doctors are much readier to send patients in early than they used to be), we believe that serial plasters are the best, simplest and least traumatic way of correcting these deformities. With early flexion deformities we put the back shell on and anchor it in place with three or sometimes four cuffs. We are quite prepared to leave the joint alone for a week or ten days. Then we remove the cuffs and usually at this stage full correction of an early deformity can be obtained with one set of shells. Then a new plaster is made in the proper position. In some cases you may require two or even three sets, but we have abandoned all forms of forced extension, traction or turn buckles, because I am convinced that if deformities cannot be corrected by this simple serial shell method, help from the orthopaedic surgeon will be needed. Prolonged periods of extension leave a floppy knee which may be straight but is of no great use to the patient.

The simple technique of using " glassona " walking cylinders is one which we have found very valuable over the years. Sometimes no amount of quadriceps exercise or anything else will correct an instability of the knee, and every time the patient begins to use the knee again there is a traumatic effusion due to ligamentous laxity. Before considering arthrodesis we give these patients a trial of fairly prolonged immobilization in a cylinder, which is worn during weight bearing; not infrequently it can later be taken off when the knee has become more stable. In women, sometimes quite a short cylinder gives enough support to get around. They like to be able to sit down and they can slip a bivalved cylinder off; we have in fact arranged to fasten it with an adhesive, so that they do not even have any buckles to undo.

We have seen our 300 patients, treated in the way described, at regular intervals for a follow-up period of nearly ten years, and assessed functional capacity. After over nine years, when 200 of the original 282 were assessed, 20 per cent of them were functionally in grade one. That really means that they have no significant residual disability. It does not mean that they have no residual signs of disease, but they are fit and able to carry out all normal activities. Some 41 per cent have suffered moderate impairment of function, but are still able to carry out all but the heaviest of activities in the home or at work, while 27 per cent are more severely handicapped but are still able to get about and look after themselves with a little assistance from others. After this long time, with an average dura-

tion of disease of between six and seven years before admission (i.e., 15 or 16 years after the onset) only 11 per cent are confined to chair or bed and chronically crippled.

We have found that a number of factors may influence the outcome but there is no question that one of the most important is the duration of disease before admission to hospital. At the fourth assessment some nine years after discharge, those admitted to hospital within one year of the onset of symptoms had fared very much better than those admitted later in the course of the disease. Of those admitted early, 37 per cent were without residual disability, in other words in grade one, as compared with only 16 per cent of those admitted after between one year and five years and 9 per cent of those admitted more than five years after the onset. This must surely provide a strong argument for the provision of a sufficient number of beds to allow of early admission to hospital of patients with this disease. These figures have been criticized on the grounds that these patients were admitted early because they were mild cases, but this is not correct, they were admitted early because every physician seeing them thought they were so ill that they must be admitted at once; in fact this acute onset seems to carry with it a rather benign prognosis.

This conservative regimen is fairly widely accepted amongst rheumatologists with beds at their disposal, but before going on to consider the use of other remedies, such as gold or steroids, I would like to consider one aspect of the regimen. It has been long accepted by the majority of physicians that rest in bed plays an important part in the treatment of rheumatoid arthritis, especially during the active phase of the disease, but there is very much less agreement as to the correct treatment of the inflamed joints during this phase. There can be no doubt that prolonged rest in bed without adequate measures to protect the painful joints and prevent the deformities can lead to disastrous results. On the other hand, the imposition of movements on inflamed joints has been roundly condemned by such men as Hunter, Thomas, Phelps, and Sir Robert Jones. My own experience up to the early 1950s had encouraged me to believe that continuous immobilization for periods up to one to three weeks often resulted in considerable benefit. Proper care of the inflamed joints in the acute phase may well have an important bearing on control of the systemic features of the disease. A number of people have begun to reconsider the view that immobilization is absolutely unethical and just asking for ankylosis.

We have carried out a trial to try and answer this question in a little more scientific way, and patients with definite rheumatoid arthritis who were admitted to the unit over a period were allocated at random to two forms of treatment. All were given the basic

calcium aspirin; in one group the joints of all four limbs, with the exception of the hips and shoulders, were completely immobilized in long plaster splints, applied from fingertips to the shoulder, and fixed in position by three cuffs, and along the backs of the legs from the toes up. I am sure my orthopaedic colleagues will roundly condemn me for having put inflamed fingers in a splint and left them like that for four weeks. During this four weeks' immobilization no other form of treatment was used. There were no maintenance exercises or static contractions. The control group were confined to bed for four weeks but were allowed up to the toilet, and splints were removed in the orthodox way twice daily for active exercises of affected joints. At the end of four weeks, complete immobilization was terminated in the rest group and thereafter both groups were treated along similar lines. Weight bearing was resumed, and active forms of physiotherapy were employed. Changes in the range of joint movement were measured initially and after 12 and 24 weeks. There was no significant diminution in the mean range of movement in the wrists, elbows, knees, and ankles in the immobilized patients. Mean values however, may conceal gains or losses in individual joints, and so data in respect of the knee joints were analysed. In only two of 29 knees with a normal range of movement before immobilization was there a loss of more than 20 degrees, and in both instances it was at the expense of flexion and without effect on function. Of 35 joints with initial impairment, range of movement increased in 19 after the period of splintage, compared with 14 in the exercise group; in other words the immobilized ones did a bit better. The results were exactly the same in the elbow joint. Immobilization might be expected to lead to diminution of muscle power, and we used strength of grip both as an index of muscle power and as a test of hand function. The initial values for grip were fairly comparable. By the twelfth week there was substantial improvement in both groups, but it was more marked in the rest group. This was rather surprising.

This trial indicates that it may well be worth while examining certain aspects of the conservative regime, the use of which has become hallowed by tradition. The most important point which emerges is that complete immobilization of affected joints in rheumatoid arthritis for four weeks was followed only by the most transient loss of movement and power in the great majority of patients; at follow-up after 24 weeks the advantage in terms of functional capacity, disease activity and strength of grip lay with those patients initially immobilized for four weeks. I do not want to advocate this as a method of treatment. I hope I made it clear initially that this was a clinical experiment to find out whether in fact immobilization led to the disastrous results we have always been told about in the

past. I would maintain as a result of this piece of work that immobilization for one week, two weeks, or three weeks can be very useful indeed in bringing acute symptoms under control, relieving pain and markedly reducing the need for analgesics and hypnotics, and that little harm has come to any of these people.

I do not intend to review the vast literature on the use of drugs in the treatment of rheumatoid arthritis, but I will try to give you a brief personal appraisal of the position. I remain convinced that aspirin is still the most effective of the so-called analgesic, anti-inflammatory group of drugs, in spite of having just attended a symposium on salicylates, a very large part of which was devoted to describing the gastro-intestinal complications which may follow the use of aspirin. In my unit we have co-operated with the drug industry and screened many compounds considered promising in preliminary work in animals, sometimes reported to be eight to ten times as potent as aspirin in the standard tests for anti-inflammatory activity. None up to the present time has proved as effective in these trials as aspirin. It is perhaps of some interest to mention that of all the tests used in these trials, strength of grip has consistently proved the most sensitive. There is no doubt that aspirin does cause gastro-intestinal bleeding, but rarely in amounts large enough to cause anaemia or deplete the iron stores. Phenylbutazone and oxyphenbutazone do not cause such bleeding, but they have their own side-effects and risks with which you are familiar. We ought to bear in mind the fact that the salicylate group, and aspirin in particular perhaps, can cause bleeding and may on occasion give rise to a chronic iron-deficiency anaemia. They can also cause acute haemorrhage, but we should not exaggerate this risk or let the idea get across to our patients that aspirin is a dangerous drug, and thus induce them to stop using it. I think this would be tragic. There is no reason at all why this sort of information should not stimulate our colleagues in the drug industry to produce something as good as aspirin that does not cause gastro-intestinal bleeding. Until they do, do not let us throw aspirin out of the window.

Steroids and corticotrophin must be classed as non-specific, anti-inflammatory drugs. Controlled trials have shown cortisone in tolerable doses to be no more effective than aspirin in controlling symptoms of the disease. Prednisone and prednisolone have certainly shown some superiority, both in respect of symptom control and perhaps in delaying, at least in the early phases of such trials, the advance of radiological change, but at the end of three years this advantage had certainly begun to decrease, and we are all becoming familiar with the late side-effects of long-term hormonal treatment, even given well within the accepted clinical dose. These are the increas-

ing incidence of spontaneous bruising, thinning of the skin, risk of collapse under stress, increasing osteoporosis, a rising diastolic pressure, persistent moon-face, hirsutism, troublesome obesity, myopathy, and neuropathy. None of the newer analogues seems to have a significant advantage over prednisolone. Similar disadvantages attend the use of corticotrophin, apart from the need for repeated injections and the possibility of acquired resistance to the hormone. Have these hormones any place in the treatment of rheumatoid arthritis? The use of intra-articular injections of steroids, applied with common sense and discretion, has an undoubted place in controlling acute local inflammation, both in the joint capsules and in soft-tissue lesions, but another possibility may be worthy of consideration. The use of steroids or corticotrophin to attain an immediate suppression of activity during the early weeks until a delayed-action drug such as gold or chloroquine takes effect, might be of some value. Before we abandon steroids or ACTH altogether, we are exploring this possibility at the present time.

Recently, the first acceptable controlled trial of gold has given it a certain air of respectability. It has shown quite clearly that this drug is of moderate value in the treatment of fairly early active cases of rheumatoid arthritis. Improvement in the treated group took place from the third month onwards and was maintained, although in reduced degree, for one year after the last injection. Of the gold-treated group 43 per cent were in the top functional grade, grade one, whereas this included only 25 per cent of the controls. In the two top grades together, gold had 85 per cent and controls 74 per cent, so we cannot deny the efficacy of this rather maligned drug. Radiological progression was not affected, but the sheep-cell agglutination test more commonly became less positive in the treated group than in controls. Complications appeared in 35 per cent of treated patients and in 16 per cent of controls. These were mainly skin reactions and seldom serious. It remains to be seen how long this improvement lasts, but the last assessment of this group of patients showed that the advantage again was diminishing and was perhaps not really as worth while as one had hoped.

There have been many reports on the use of chloroquine and hydroxychloroquine in rheumatoid arthritis since 1951. Few of these trials have been adequately controlled, but recently from Professor Kellgren's unit the results of a double-blind trial of 134 patients with rheumatoid arthritis given 250 mg. chloroquine daily have shown a significantly greater improvement among treated patients in terms of clinical and laboratory criteria than in controls. Again, unfortunately, a similar degree of radiological progression took place in both groups. There was a significant and interesting correlation between decrease in the sheep-cell titre and clinical improvement.

These authors conclude that chloroquine may be of some value as an adjunct to conservative treatment in rheumatoid arthritis. It certainly has the advantage over gold of being easily administered, while supervision of treatment rarely causes the general practitioner much anxiety. We are now aware of the minimal risk of corneal opacities due to deposition of the drug in the cornea, and the rarer but much more serious risk of irreversible retinal damage.

Intravenous administration of saccharated oxide of iron in courses of up to 2—3 G. to patients with rheumatoid arthritis has seemed to be of very definite benefit, in our hands at least. The treated group showed a significantly greater improvement as regards anaemia than a matched group of controls. A rise in haemoglobin value was associated with a fall in the mean E.S.R. level; functional capacity improved and disease activity diminished simultaneously. Improvement in anaemia in the treated patients was due mainly to a rise in the red cell count and not to a correction of the hypochromia, so I do not think we are simply seeing the correction of an iron-deficiency anaemia. There is some other action. Perhaps colloidal suspensions other than iron might have the same effect. From the results of this study it would seem that the therapeutic effect of saccharated oxide of iron is not directly dependent on its iron content, but that in the majority of cases beneficial effects follow as a result of reduction in disease activity.

In conclusion, it may be opportune to pause and take stock before we embark on further clinical trials which those of us who have been doing them for the last ten years now regard with the greatest distaste and weariness. In spite of the most intensive period of basic and clinical research in the whole history of rheumatic diseases during the last ten years, the cause of this crippling disease remains obscure though we do know a good bit more about its natural course, and now recognize certain factors with a bearing on prognosis. No single remedy is satisfactory, but a number of methods of treatment have been shown to ameliorate symptoms and reduce disease activity. A combination of local and general rest, combined with full doses of aspirin and carefully graduated activity, is the backbone of treatment. Response is much more satisfactory in the early stages of the disease, and this means that we have got to insist on an adequate number of beds for the treatment of these cases, especially at the stage when no real irreversible damage has taken place and where there is every prospect of inducing not a cure but a long remission. It is easier to establish good habits in a patient in hospital and to persuade her that splints are not a nuisance but are comfortable and that a little exercise is important. You can send the physiotherapist to their home, and you can fix them up with a weight and pulley very easily.

You can send the occupational therapist to their kitchen, so that she can give them advice on rearranging their equipment. Intravenous iron in our hands seems to be of value. Gold and chloroquine may be of some definite value, but you have got to accept a certain amount of risk.

It is possible to use steroids or corticotrophin to help the situation at any stage in treatment? It seems to me that there is certainly room for further experiment, and we are at the moment conducting such an experiment. It is going to be very difficult, however, to assess the result, but what we are doing is this: we are putting the active joints in plaster by the method we have demonstrated, and we have reduced the period of immobilization to three weeks instead of four. We are using soluble aspirin and saccharated oxide of iron (after a test dose of 50 mg. we give a total of 3 G.). We are using corticotrophin, 40 units daily for the first two weeks, 30 units daily for the next week and 20 units daily for a further week, with gradual withdrawal. Up to now this combined course has induced the most striking remissions, but I do not think they will persist. However, you certainly get off to a flying start with this combination. At the same time we give chloroquine 250 mg. daily. In other words, we are giving to these patients a number of those remedies which have been by themselves established as effective. Why not put them together? Why not try and give the patient the benefit of all our ten years' clinical trials? Anyway, this is what we are doing. I regard our unit as the sort of place where this kind of thing can be tried out. We are certainly ready to modify this approach at any time in the light of experience or new knowledge, but for the present I feel it is not altogether illogical to combine methods which have themselves been subjected to controlled clinical trials. Only time will tell whether combined application achieves more rapid and more lasting control of disease activity than has been possible in the past.