

Those with predominant but never exclusive involvement of the terminal finger joint, usually associated with changes in the nail of the same finger; they are serologically negative. There may be a swollen finger with loss of the skin markings—a sort of dactylitis, again serologically negative. (2) Those with a much more severe process which produces loss of movement in the spine and changes in the sacroiliac joints much the same as those in ankylosing spondylitis; unlike ankylosing spondylitis, it produces severe deformity often with ankylosis in peripheral joints. Many of the finger joints become deformed and ankylosed. (3) Those cases indistinguishable from rheumatoid arthritis although the majority are sero-negative.

The *Stevens Johnson* syndrome produces acute effusions, particularly in large joints. It is sometimes associated with the rash of *erythema multiforme*, always with ulceration in the mouth and genital tract; the mouth ulcers are accompanied by sloughing, unlike those of Behçet's syndrome which we come to next.

*Behçet's syndromè*, originally described as a combination of orogenital ulceration with relapsing iritis, is now expanded to include skin lesions, other eye lesions, lesions of the central nervous system, thrombophlebitis migrans, and arthropathy (occurring in 64 per cent). The onset is acute, often affecting only a single joint and settling without residual trouble.

## Choice of drugs in the treatment of rheumatoid arthritis

**Dr Dudley Hart, M.D., F.R.C.P.** (*Consultant physician, Westminster Hospital and Medical School*)

There are many potential drugs for the treatment of rheumatoid disease, but what are we treating in this disorder? Pain in rheumatoid arthritis is but one of the symptoms. There is also a psychological or spiritual illness and a deep depression, with feelings of hopelessness in seeing no future and feeling thwarted, of incapability to work or play adequately, and of anxiety concerning the future. In addition to the pain in many joints, this attitude covers and colours the whole picture.

Patients get an overall feeling of illness with rheumatoid arthritis; they are systemically ill as well as arthritically ill; they ache all over, feel weak and feeble, have no drive and have certain features slightly suggestive of an Addisonian or pseudo-Addisonian state. Fever and tachycardia are present and their libido is absent or diminished.

In addition, local pain may be felt in nearly all the joints, and these can be referred widely so that the pain in an elbow can fan up to the shoulder and down to the wrist; the important triad is weakness, swelling and stiffness with pain in a given area. Analgesics help this local pain, but they may not help other features much. Antidepressants may help the depressive aspect and corticosteroids help as anti-inflammatory agents but not as analgesics. We recently asked 100 patients what they thought of alcohol in terms of their rheumatoid arthritis; some said it made them feel worse and they never touched it, but the majority found that the occasional drink helped. It has always been of interest to me that there are so few alcoholic arthritics, although there is nothing to stop an alcoholic becoming arthritic.

### *Relief of pain*

The relief of pain and drug administration is only one part of the general management. Of the analgesics at your disposal, the first to try are the salicylates. We put

aspirin first; the patient is given aspirin in one of its many forms and if he gets better and tolerates the aspirin, whatever the type of arthritis, this is the answer. But aspirin is an anti-inflammatory agent only if given in doses of something like 5 gm or more a day (that is, 15 tablets); below this, little anti-inflammatory action is demonstrated but you can show an analgesic action. So with between five and eight tablets a day there is some pain relief, but that is as far as it goes. If you wish to use aspirin as an anti-rheumatic agent you must administer more than 5 gm a day, and if you want to obtain a really effective blood level of over 25 mg per 100 ml, you may have to go a good deal higher than that. You can either use the drug *prn* as an analgesic or regularly as an anti-inflammatory agent, giving the patient about 1 gm every three, four or five hours throughout the day. There are many different sorts of aspirin, so I will run briefly through the list. Many patients say that they cannot take ordinary aspirin because they get indigestion and they much prefer soluble aspirin (Solprin or Disprin). In addition, there are glycinated preparations such as Paynocil, containing aminoacetic acid, that is, glycine, with 600 mg aspirin. These tablets contain twice as much aspirin as the ordinary tablet, they have a slightly sweet flavour due to the sweetness of glycine, which has a lemonish flavour; some patients like it, but many do not. A buffered aspirin may be used but there is not much evidence that buffered aspirin has a less toxic effect on the gastro-intestinal tract than unbuffered aspirin. In this preparation aspirin is buffered with dihydroxyaluminium aminoacetate and magnesium carbonate, and though some patients prefer it to the others, most are perfectly happy with ordinary soluble aspirin. There is one product, aloxiprin—Palaprin—a condensation product of aluminium oxide and aspirin, which has been shown to be somewhat less likely to produce bleeding from the alimentary tract than most other forms. Aspirin mixtures are much more irritating. They should be dispensed fresh, as they deteriorate, causing a good deal of gastro-intestinal irritation. Old-fashioned powders, including Beecham's (a mixture of phenacetin and aspirin), get moist and deteriorate and may cause gastro-intestinal irritation. There is one old-fashioned mixture which is popular, particularly in the cancer departments of the land, and that is *Mist. Aspirin. Opiat*, containing from 10 to 20 minims (0.6–1.2 ml) of tincture of opium in about a gram of aspirin in fluid form. This should be dispensed fresh. Our pharmacist recently said that although pharmaceutically the mixture was a bad thing, people seemed to tolerate it well, but on the next day a patient developed a violent haematemesis after taking it. You can make a similar mixture by using 1.5 gm of paracetamol instead of aspirin and this does not have the same disadvantage. Paracetamol is often used because it is relatively benign and is less likely to upset the patient's interior. It is not a powerful drug, but it has become increasingly popular and in doses of between 1 and 2 gm it has helped a lot of patients who cannot tolerate any of the forms of aspirin.

The Ministry of Health has sent out a list of the comparative costs of various drugs commonly prescribed for painful osteoarthritis. It gives the total NHS cost of 50 tablets or capsules, but it does not give a full day's treatment cost. If we break the figures down to a full day's treatment—this is totally unrelated to the fact that Geigy is helping us today—a day's treatment of three tablets of phenylbutazone works out at 4½d. The next cheapest is Butazolidin itself at 5d by current MIMS prices, and aspirin is third if you use 5 gm per day, at 10d to 1/-. After that comes soluble aspirin at 1/- to 1/2, then paracetamol at 1/3d and indomethacin is the most expensive at 1/4½d for three per day. The range of 4½d to 1/4½d a day, is not frightful for a patient suffering from a painful and crippling disorder.

At the Westminster we have not used phenacetin since 1955. There is evidence that compound tablets containing phenacetin produce necrotic change in the papillae of the kidney, and there is no doubt that it can cause enterogenous cyanosis, sulphaemoglobin-aemia and methaemoglobinaemia. There is no place for phenacetin any more because

as an analgesic it is no better than the others and it has these unpleasant side-effects. Paracetamol is relatively mild, and although it is similar structurally to phenacetin, there is no case against it. Dihydrocodeine bitartrate is useful, whether given by injection or as tablets. Codeine constipates and is seldom used except as a compound tablet, and codeine itself is of little value as an analgesic in the small doses in which it is used.

#### *Other anti-inflammatory agents*

Paracetamol, codeine and dihydrocodeine appear to be analgesic but they do not reduce swelling and inflammation. Aspirin, given in the right amount, does reduce inflammatory swelling, and so do mefenamic acid (Ponstan) and flufenamic acid (Arlief 100).

The disadvantage of mefenamic acid and flufenamic acid is their tendency to cause diarrhoea. They are analgesic, they are anti-inflammatory and they can usefully be tried in patients who cannot tolerate any of the more common drugs. Of the two, flufenamic acid has more to offer than mefenamic acid in relief of symptoms and is less likely to produce side-effects. Among the pyrazoles we have phenylbutazone (Butazolidin) and oxyphenbutazone (Tanderil). There is also nifenazone (Thylin) but in our trial at the clinic we found it to be no better than a placebo. Phenylbutazone and oxyphenbutazone are useful inasmuch as they are anti-inflammatory and relieve pain; they do this in a long-acting even way; they have a long half-life, and are slowly broken down. There is no particular virtue in giving more than 300/400 mg a day because higher doses do not usually enhance the effect, although some patients do need and tolerate bigger doses. The main snag about phenylbutazone and oxyphenbutazone is the remote chance of their causing a blood dyscrasia. Several cases of agranulocytosis, thrombocytopenic purpura and aplastic anaemia due to these drugs have been recorded, but they are rare complications, perhaps a 1 in 50,000 chance. Gastro-intestinal upsets, skin rashes, and oedema can also be a nuisance.

Dr Andrew Herxheimer pointed out to me recently that the cheapest of the full day's anti-inflammatory analgesic treatments now is phenylbutazone. The most expensive is indomethacin, an anti-inflammatory analgesic and antipyretic substance. Its snags you all know well enough; it causes swimmy headaches, muzzy sensations and peculiar feelings in the head and this is a dose-related manifestation occurring when doses are increased. There is great individual variation in tolerance. Some patients will tolerate ten capsules a day and have no side effects, others will develop side effects on two or three. Indomethacin is largely excreted in the urine. It should not be given to patients with faulty renal function or raised blood urea because they are much more likely to get high blood levels and suffer side-effects. Indomethacin also causes gastro-intestinal upsets. It can, like aspirin and phenylbutazone be associated with hematemesis or malaena but the commonest side-effect of indomethacin is this swimmy headache sensation. Blood dyscrasias have occurred, but it has not been proven that there is any relation to administration of the drug.

#### *Side effects*

Perhaps at this point I might say a few words regarding side effects of the more commonly used analgesic and anti-inflammatory drugs. As you know, it was the rising incidence of liver trouble and jaundice reported to the Committee on Safety of Drugs that led to the withdrawal of Ibufenac. With regard to mefenamic acid (Ponstan), there has been no important change in the general pattern of adverse reactions and the total number of cases of gastro-intestinal haemorrhage stands at eight during a four-year period; there have been the usual expected number of reports of diarrhoea. We should regard diarrhoea as an absolute contraindication for continuing treatment with Ponstan. Rashes and minor central nervous system effects are also reported. Flufenamic acid (Arlief 100) hardly featured in the register of adverse reactions, but diarrhoea has been

the main trouble and one case of gastro-intestinal haemorrhage has been reported. The most widely used drugs always have the highest incidence of side effects; this automatically follows, since if a drug is not used much then the incidence of side effects is lowest. One interesting development has been a few reports of a Coombs-positive haemolytic anaemia, apparently identical to that which occurs with methyl dopa, in patients receiving Ponstan and it is likely that these are causally related to the drug. More recently still there has been a case of haemolytic anaemia with a strongly positive Coombs test in a patient receiving flufenamic acid, but there is less certainty in this case regarding the etiology. With regard to indomethacin, the interest in reporting reactions has declined, thus the number of reported side effects has diminished. The number of cases of blood dyscrasias reported is small in relation to phenylbutazone, but there have been some reports of thrombocytopenia with two fatal cases, and seven of aplastic anaemia with fatal results in two cases. But it is difficult in these cases to be sure that the blood dyscrasia was not due to previous treatment with phenylbutazone or oxyphenbutazone. Indomethacin may occasionally produce acute psychotic reactions which generally manifest as acute depression or confusion with hallucinations.

In MIMS you will find that in the anti-inflammatory and analgesic section there are more than 100 compounds but the majority of these are mixtures of one sort or another, and it is quite extraordinary how the aspirin, phenacetin, caffeine and codeine mixtures which crept into therapy many years ago are still there. They sell well, mostly across the chemist's counter, but there is no particular evidence that they are any better than any other single cheaper substances. As regards other routes of administration, dihydrocodeine (DF 118) and certain other substances can be given by intramuscular injection, and there are suppositories that are particularly useful at night to reduce morning stiffness in rheumatoid arthritis. Indomethacin is available as a 100 mg suppository, and there are 250 mg suppositories of phenylbutazone and oxyphenbutazone. These have a useful place in controlling nocturnal symptoms in patients who have much pain at night and experience morning stiffness.

Dextropropoxyphene is analgesic and not anti-inflammatory. It is available in many mixtures or by itself. Doloxene contains 65 mg dextropropoxyphene and Depronal 150 mg without any other added analgesic substances.

### *Gold and antimalarials*

Two other long-acting drugs that can be used in the treatment of rheumatoid arthritis are gold salts and the antimalarials. Gold (sodium aurothiomalate, Myocrisin) is useful and has been shown to produce good therapeutic effects but always with the risk of certain well-known side-effects; one third of patients on gold salts develop dermatitis of some sort, and within the last six months a lady I had not seen for many months died from aplastic anaemia. She had been treated with gold perfectly correctly but her platelets suddenly disappeared from the circulating blood without warning signs in routine blood counts. Nowadays, few doctors give more than 50 mg by injection at a time, and as the patient improves and the sedimentation rate comes down, and the general picture improves, the amount of gold is lessened or spaced more widely. The antimalarials, chloroquine and hydroxychloroquine, are less popular than they were, possibly because of the knowledge that they can cause certain permanent retinal changes.

The immunosuppressive agents are still in the realm of experimental rather than orthodox therapeutics. After all, patients with rheumatoid arthritis and with other types of arthritis do not commonly die of their disease. I think it is interesting to examine the figures that Dr Verna Wright produced in the book edited by Dr Hill where, of 32 deaths in psoriatic arthropathy, 15 were associated with corticosteroid treatment. In other words, half the mortality was associated with one particular form of therapy.

Before administering immunosuppressive agents in any disorder one must first

consider whether the treatment is likely to prove more fatal than the disease.

Antidepressants and stimulants may be usefully employed, and occasionally a mixture of amylobarbitone and dextroamphetamine does get the patient through an unhappy flat period. Antidepressants, such as imipramine or amitriptyline are sometimes as useful as, if not more than, other official antirheumatic drugs. Patients may derive benefit from a small dose of a barbiturate or some other form of sedative and recently we have been rather impressed with diazepam (Valium) and to a less extent chlordiazepoxide (Librium).

Let us now consider the corticosteroids. Dr A. G. S. Hill has emphasized how a modest evening dose of 5–6 mg will maintain its effect throughout the night and relieve the patient's feeling of morning stiffness. Unpleasant hormonal overtones do not arise at this dosage level but will become evident if higher doses are administered over many months. However, if you can improve the patient's condition by giving no more than 6 mg of prednisone or prednisolone daily, that is legitimate treatment. In the potentially fatal disorders, such as *disseminated lupus erythematosus* one may increase the dosage as high as is necessary to control the disease.

In the selection of drugs, I have always been greatly aware of the 'choosey' patient, who says "I can take aspirin—but not Disprin", and so on; the same degree of selectivity applies equally to the doctor when he is making his own choice for the patient. There are doctors who are 'codeine-positive' or 'ibufenac-positive' or 'indomethacin-negative' towards various drugs. This favouritism often applies to substances which have different titles but which are the same substance.

As far as the ordinary analgesic, anti-inflammatory agents are concerned, there are no hard and fast rules for selecting the right one. My own choice depends on the particular conditions of each individual case.

## Gout

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Gout, as you know, has been described and recognized for over 2,000 years and I cannot in this short space of time cover such a noble lineage completely.

The manifestations of gouty arthritis, chronic and acute, can be related to the presence of excess quantities of uric acid or urate in its solid form in the tissues. Since urate was first isolated from tissues nearly 200 years ago, there has been no question that the manifestations of chronic gouty arthritis are due to its presence. If the solid deposits which are present in gouty arthritis are examined under a microscope or chemically analysed they are seen to consist of urate crystals. Garrod's original view that uric acid was the cause of the acute attack was however questioned for many years, and there were certain reasons for this. Colchicine, which is so effective in relieving the acute attack, does not lower the uric acid level in the blood, and some people, such as the relatives of a gouty patient, may have a high uric acid level for a long time without developing gout. More recently it has been found that urate crystals can always be detected in the joint fluid of acute gouty arthritis. It has also been shown that injecting