PAPERS AND ORIGINALS

Inflammatory disease and its control in rheumatic disorders*

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Inflammation is a central and essential component in most forms of arthritis—for instance, rheumatoid arthritis, acute gout, Reiter's disease, and even osteoarthritis. The inflammatory changes are different in these various disorders. The underlying pathological processes produce entirely different changes in the body and the resulting clinical syndromes are entirely dissimilar. It follows that attempts to control the inflammatory changes have different effects on the different rheumatic disorders.

Let us take four different rheumatic disorders—gout, ankylosing spondylitis, rheumatoid arthritis, and polymyalgia arteritica—and discuss what part inflammation plays in their symptomatology. In none does inflammation seem to have any useful function. With all due respect to mother nature the inflammatory process she puts there, presumably to perform some useful function initially, is now the disease itself in greater or lesser degree. It is inflammation that causes the local joint pain, tenderness, swelling, and stiffness and also the systemic illness that goes with it. In attempting to suppress this inflammation we are doing nothing but good unless bacteria are present in the tissues. So had we a perfect non-toxic and highly effective anti-inflammatory agent, by suppressing inflammatory change we would eliminate much of the pain, swelling, stiffness, tenderness, and disability in many rheumatic disorders, even if we did not cure the disease.

Gout

There is general agreement today that the intense discomfort of acute gout is due to deposition of crystals of monosodium urate in the tissues, which sets up an intense and acute inflammatory reaction. Seegmiller and Howell¹ suggested that three requirements were necessary for an acute attack of gout: (a) deposition in the tissues of crystals of monosodium urate; (b) development of an inflammatory

reaction directed against the crystals; and (c) propagation of the inflammatory response by the addition of further crystals in the area of inflammation. But obviously many other factors are involved. What biological factors precipitate this deposition of crystals, and why do some attacks abate spontaneously and others run on for several weeks?

Van Arman *et al*² showed that when precautions were taken to prevent any possible endotoxin contamination of urate crystals that were injected into the knee joints of dogs the crystals became significantly less active. Endotoxin derived from *Escherichia coli* by itself caused pain and leucocyte infiltration into the joint, and a small dose of urate crystals which caused no pain by itself became very painful when the crystals were allowed to absorb endotoxin in vitro. When the same small non-painful dose of crystals was injected into the joint and the dog given endotoxin by mouth pain became clearly evident. This work suggests that it may not be the crystals alone but substances absorbed on to them that cause the disruption of leucocytes, which in turn causes the intense pain of acute gout.

TREATMENT OF ACUTE GOUT

Whatever the trigger that starts off the attack, once initiated the essence of the treatment of acute gout is to give the maximum tolerated dose of the selected drug as soon as possible after the onset of the attack. The popular drugs are indomethacin, phenylbutazone and oxyphenbutazone, with colchicine in third place. In addition to early treatment the other essentials for rapid and effective control are a high initial dose and 24-hour cover for two to four days; apparent resistance to treatment is often due to too little being given too late.

With indomethacin night cover with a 100-mg suppository is effective and by day either a 100-mg suppository or 100-150 mg with food by mouth in divided doses is sufficient; seldom is it necessary to give more than this and seldom is it tolerated, for dose-related effects—headaches and various cerebral sensations—will limit the amount given. It is important, therefore, to test the tolerance of a patient to a therapeutic agent beforehand, for one drug may be well tolerated by one patient and ill tolerated by another. As indomethacin is excreted in the urine impaired renal function may be responsible for toxic reactions at low dose levels. Phenylbutazone or oxyphenbutazone is also highly effective; 600-800 mg in divided doses should be given by mouth on day 1, with subsequent reductions by 100-200 mg daily over four to five days. Boardman and Hart³ found indomethacin rather quicker in action than phenylbutazone and therefore marginally preferable, both drugs proving superior to colchicine. Smyth and Percy⁴ claimed the two drugs were equally effective.

Wolfson and Robinson⁵ noted in 1951 that in acute gout the

*Based on the Bradshaw lecture delivered at the Warwickshire Postgraduate Medical Centre on 18 September 1975.

asymptomatic contralateral member also swelled as a result of increased blood flow; Smyth and Percy⁴ found reduction of swelling in both extremities on indomethacin, but with phenylbutazone there was less swelling of the affected member and an actual increase in swelling of the unaffected member, probably due to the sodium-retaining nature of the drug. This is a theoretical rather than a practical disadvantage unless the patient is in borderline cardiac failure, when congestive failure may be precipitated by phenylbutazone or oxyphenbutazone. On short-term treatment toxic changes in the blood are extremely unlikely on these drugs.

The newer anti-inflammatory agents have not proved their worth in gout, but there are reports of naproxen^{6,7} and ketoprofen⁸ being effective in some cases. Colchicine, not an anti-inflammatory agent except in gout, is still popular with a minority of patients. It is of interest that the most effective anti-inflammatory agents we have—the corticosteroids, corticotrophin, and tetracosactrin—are on the whole less satisfactory than the non-steroidal agents, relapse occurring more quickly on discontinuing treatment; but they are often effective at high doses in resistant cases when other agents have failed.

Action of anti-inflammatory agents—How do these anti-inflammatory agents work? Indomethacin and aspirin are potent inhibitors of prostaglandin synthetase, but the corticosteroids are not. Aspirin is of little help in acute gout, though in full doses it is an effective anti-inflammatory agent. Though much is known about the inflammatory reaction in gout little is known about why some agents work so much better than others. But as a clinical model of reversible acute inflammation the patient with gout is second to none, and an effective anti-inflammatory agent can be seen (and felt) to work within 48 hours in most cases.

Ankylosing spondylitis

Ankylosing spondylitis has, in this country at least, long been considered a very different disorder from rheumatoid arthritis in that it affects men rather than women and starts in youth rather than in middle age and because it produces an entirely different clinical picture. There are no nodules, arteritis, or rheumatoid factor in the serum, and the condition has a different mode of progression, a different prognosis, different responses to many forms of treatment, and different complications. Histological similarities in peripheral joints, when affected, are hardly enough to warrant a common diagnosis, but for years in the United States of America it was considered a variant of rheumatoid disease and was labelled rheumatoid spondylitis. It is now considered a disorder in its own right, for Ball⁹ and others have described an underlying pathology different from that of rheumatoid arthritis, and Brewerton *et al*¹⁰ and Schlosstein *et al*¹¹ and others have shown that whether apparently idiopathic or secondary to psoriasis, Reiter's disease, ulcerative colitis, different forms of dysentery, or other disorders patients with ankylosing spondylitis usually have the tissue antigen HL-A 27.

THE INFLAMMATORY PROCESS

The inflammatory process in ankylosing spondylitis is what concerns us today. Starting insidiously as an ache in the sacroiliac region, buttock, or back it tends to progress with increasing stiffness of spine, girdle joints, and thorax, producing an end result completely unlike that of rheumatoid disease. Niepel *et al*¹² in 1966 first used the term enthesiopathy, and Ball drew attention in his Heberden oration⁹ to the importance of pathological changes occurring in the ligamentous attachment, the enthesis.

The enthesis is a metabolically active site, at least during growth, a point of probable significance in this disease of late adolescence and young adult life. Multiple, focal, microscopic, and inflammatory lesions are localised to the ligamentous attachments. Destructive changes and erosions and defects are present in the cortical bone, and, though neutrophil polymorphonuclear leucocytes are prominent in some lesions, lymphocytes and plasma cells predominate in most, concentrated in the central part of the erosions and spreading along the path of small vessels in the ligaments. These erosive lesions heal by deposition of reactive bone in finely fibrous connective tissue without preceding cartilage formation. The new bone tends to fill in the cortical defect, joining the deeper bone to the eroded end of the ligament, thus forming a new enthesis above the original level of the cortical surface.

In the spine erosive lesions are seen at anterior or anterolateral

attachments of the outer annulus at or just below the annular flange and the corner of the vertebral body, sometimes in both sites, but similar changes occur in extra-spinal sites, such as the patella, iliac crests, and greater trochanter. In the sacroiliac joints, as in the spinal apophyseal joints, a peripheral shell of bone encloses articular cartilages showing only evidence of old enchondral ossification.

DISTINGUISHING FEATURES OF THE CONDITION

Ball's⁹ definition of the difference between the spondylitis seen occasionally in rheumatoid arthritis and that seen commonly in ankylosing spondylitis may be summarised as follows:

Rheumatoid spondylitis is essentially a special type of erosive synovitis, whereas ankylosing spondylitis is a less destructive erosive synovitis with in addition a striking inflammatory enthesiopathy with a tendency to fusion with ossification. In the intervertebral disc and the apophyseal spinal and the manubriosternal joints ossification is initiated and promoted by lesions at ligamentous attachments, and when this has produced ankylosis the remainder of the joint is partly or completely replaced by enchondral ossification. In ankylosing spondylitis, therefore, the inflammatory basis has a different form, a different mode of progression and a different end result from that seen in rheumatoid disease.

The clinical differences are pronounced. Inflammation proceeds to fusion and ankylosis, particularly if the patient is rested overmuch or immobilised, so that in an immobile patient with severe disease total fusion occurs and the patient becomes a human ramrod. In addition, tenderness may occur at tendinous insertions into ischial tuberosities, spine, iliac crests, heels, and elsewhere; the effects on thoracic function of rib fusion on to ribs and transverse processes have long been appreciated. Increased stiffness leads to impaired mobility and an increased liability to injuries, major or minor, particularly in the cervical spine, which may snap like a long bone. Iritis is common.

TREATMENT

The role of anti-inflammatory agents is to ease pain and stiffness sufficiently for the patient to keep actively mobile by day, to continue exercises effectively and efficiently, and to go through the night without prolonged stiffness in the morning. Deep x-ray treatment applied locally to the spine in conservative skin dose of 1000 R or less is helpful, but because of the risk of leukaemia is now reserved for patients not responding to other measures. Applied locally to—for example, heels or iliac crests—in skin doses of 200–400 R this treatment is still often more helpful than any other in relieving tenderness in these areas.

Drugs

Phenylbutazone became available at the time (1952) when the hazards of deep x-ray treatment became fully appreciated. With its long even action it would probably be the drug of choice but for the risk, which it shares with oxyphenbutazone, of causing a blood dyscrasia when continued for several weeks or months. Hence when indomethacin was introduced 14 years later many patients were changed to or started on this drug. Having a shorter duration of action than phenylbutazone or oxyphenbutazone, it has to be given as a loading dose or in suppository form at night and at regular intervals in the day. Corticosteroids are in general reserved for patients with severe disease in active phases and occasional selected patients with peripheral joint changes. In conservative dosage—that is, prednisolone in doses of less than 7 mg/day—a corticosteroid is often no more and is usually less helpful than the non-steroidal agents. Some of the newer agents, such as naproxen,¹³ flurbiprofen,^{14,15} and ibuprofen,¹⁶ have been reported as helpful, but usually only the milder cases are helped by moderate doses of aspirin or simple analgesics. Sedimentation rates are little affected and symptomatic ease with better function and exercise capacity is the aim.

With encouragement and a suitable programme of exercise and exercises anti-inflammatory agents play a very real part in the treatment of ankylosing spondylitis. Follow-up of 27 of my patients showed that 14 had as good a spinal range of movement, or better, than they had initially, 10 to 27 years earlier.¹⁷ Thus, by reducing pain and stiffness

by day and by night in spine and girdle joints, effective anti-inflammatory treatment materially helps the programme of mobility and exercise so vitally necessary for these patients.

Rheumatoid arthritis

The inflammatory disease of rheumatoid arthritis is primarily of joints but may in some cases affect heart, lungs, pleura, blood vessels, and other structures. When a joint is affected intra-articular fluid increases, there is a polymorphonuclear pleocytosis, and capsule and synovium become swollen and congested. The joint fluid becomes more viscous and clots readily. The inflamed synovium proliferates and granulomatous inflammatory change, the so-called pannus, extends over the cartilaginous articular surface, which becomes gradually destroyed. Biopsy of the inflamed synovium in its earliest stages will show polymorphs dominating the scene, later lymphocytes, and later still plasma cells, responsible for the so-called rheumatoid factor. These changes are non-specific and not by themselves diagnostic of rheumatoid arthritis.¹⁸ The synovial membrane contains rheumatoid factor, immunoglobulin G, and complement components. Such immune complexes may cause inflammatory disease and tissue damage, but to date no clear evidence of an infective organism has been found in the tissues. No further attempt will be made to go into the complex background of inflammatory changes in rheumatoid arthritis except to point out that the patient becomes systemically ill, febrile, and anaemic as a result of the persistent inflammatory changes.

DESTRUCTIVE INFLAMMATORY PROCESS

Unlike ankylosing spondylitis the end results of rheumatoid arthritis are not ossification and ankylosis but destruction, increased deformity, and unnatural mobility, with occasional fibrous but only rarely bony ankylosis. Nodule formation and arteritis, present in all patients with severe rheumatism, are absent in almost all patients with spondylitis. Spondylitis is a stiffening ankylosing ligamentous hardening process, rheumatoid arthritis a ligamentous loosening and destructive one. Patients with ankylosing spondylitis are almost always of tissue type HL-A 27 (W 27); those with rheumatoid arthritis are of different tissue types, no one type dominating.

The progressive destructive inflammatory process in rheumatoid arthritis causes not only crippling but systemic illness and changes outside the joints that may prove fatal. This inflammatory process, which is in rheumatoid arthritis the disease itself, sometimes slowly settles down and, more rarely, rapidly does so. Therefore in its early stages, before crippling has occurred, it is a reversible and curable disease.

TREATMENT

What anti-inflammatory agents have we at our disposal to control or modify the pathological process? Based on our work in measuring digital swelling in rheumatoid arthritis treated with various therapeutic agents¹⁹⁻²¹ we would classify the drugs in order of efficacy as follows: group 1, the corticosteroids, corticotrophin, and tetracosactrin; group 2, high-dose aspirin (4-6 g/day) in its various forms, indomethacin, phenylbutazone, and oxyphenbutazone; group 3, low-dose aspirin (2-3.5 g/day) in its various forms; the anthranilates, mefenamic acid and flufenamic acid; the propionic acid substances, ibuprofen, naproxen, ketoprofen, and fenoprofen; and alclofenac; group 4, agents which, though their mode of action is unknown, seem to act as long term anti-inflammatory agents: gold salts, chloroquine and dihydrochloroquine, penicillamine, and the so-called immunosuppressive agents such as azathioprine and cyclophosphamide.

Although there are several new agents awaiting completion of therapeutic trials these are the drugs now at our disposal in the United Kingdom, with, in addition, several analgesic substances with no peripheral anti-inflammatory action—for example, codeine, dihydrocodeine, paracetamol, pentazocine, and dextropropoxyphene.

Effectiveness of anti-inflammatory agents

How effective are these anti-inflammatory agents? Can we effectively suppress the inflammatory process with them or not? Unfortunately,

the answer in most cases is no. We can produce symptomatic ease, better function, less stiffness, sounder sleep, and considerable pain relief, but we cannot switch off the disease and can only damp it down and hope it will go out in time of its own accord; for rheumatoid inflammatory change, like a smouldering fire, tends to settle down and disappear the more effectively it is suppressed over long periods.

In this context McConkey *et al*²² have pointed out that, though neither aspirin nor indomethacin influence the levels of the erythrocyte sedimentation rate (ESR) or two acute-phase proteins—C-reactive proteins and haptoglobin—in rheumatoid arthritis, the adrenal corticosteroids do profoundly affect the acute-phase protein response. The ESR is mainly dependent on plasma fibrinogen, itself an acute-phase protein. These workers suggest that not only are the corticosteroids more powerful anti-inflammatory agents than the non-corticosteroidal anti-inflammatory agents but they also act differently, and they state that as it has been established that the course of rheumatoid arthritis is reflected in the acute-phase protein levels, the ability of drugs to influence them implies also an ability to alter the course of the disease. They suggest that the non-steroidal anti-inflammatory agents provide symptomatic relief only and that there is no point in assessing them by any other method than clinical observation.

I would go along with this last view up to a point. The corticosteroids, being more powerful agents, can indeed influence the inflammatory disease process more completely, and at high dose levels cause not only the ESR but also the anaemia and plasma protein pattern to return to normal, but as soon as this high dose is reduced or discontinued the disease rapidly returns with raised ESR and anaemia and plasma protein changes. The action of corticosteroids is certainly deeper, more profound, and more dramatic, but it is no more lasting than that of the non-steroidal agents, and at high dose levels it is also potentially more dangerous.

When rapid anti-inflammatory action is needed in a naturally self-terminating disease, as in acute gout, corticosteroids are no more, indeed, they are rather less, effective than the non-steroidal agents indomethacin, phenylbutazone, or oxyphenbutazone and rebound attacks of gout seem to occur more often with corticosteroid treatment than with non-steroidal anti-inflammatory agents. In the inflammatory arteriopathies such as polyarteritis nodosa, polymyalgia rheumatica, and giant cell arteritis corticosteroids are the most effective agents we have, and there is evidence that though non-steroidal anti-inflammatory agents suppress inflammatory symptoms in these disorders they may not be powerful enough to stop vascular complications such as blindness or gangrene.

Serum acute-phase proteins and therapeutic effect

Recently Aylward *et al*²³ studied the effects of different therapeutic agents on serum acute-phase proteins. Neither aspirin nor indomethacin influenced the level of ESR, fibrinogen, haptoglobin, C-reactive protein, or α -1-acid-glycoprotein, but treatment with gold salts, penicillamine, and alclofenac did reduce them significantly. Moreover, after three months' continuous medication, when these three substances were discontinued, plasma tryptophan concentrations did not rapidly return to pretreatment levels as they did with the other agents, and Aylward *et al* suggest that a more profound and lasting effect on the disease process is obtained rather than a temporary anti-inflammatory effect obtained only during administration of these drugs. With gold salts and penicillamine I have been impressed by the longer duration of therapeutic effect, which takes a month or so to appear and about as long to wear off after stopping medication. But wear off it does, hence the long-term treatment programme now given with gold and penicillamine. It seems that by a more prolonged effective use of any good anti-inflammatory agent the chances of inducing a spontaneous remission are greater, and I would agree that the slow-acting more prolonged agents like penicillamine and gold are more likely to effect such a remission, but I have not had sufficient experience with alclofenac to make statements with regard to this substance.

Best use

It seems, therefore, that the best use we can make of the anti-inflammatory agents at our disposal in rheumatoid arthritis is to aim to get the maximum therapeutic effect with the most effective tolerated dose of the most effective agent in the particular patient being treated for as long as possible. One has to balance, like an actuary, the credit (therapeutic response) against the debit (toxic effects) in each case. The human patient differs greatly from the experimental animal in that apparently very similar patients will often behave entirely differently in their response to the same therapeutic agent.

Polymyalgia arteritica

By the name polymyalgia arteritica, first used by the Scandinavian workers Hamrin *et al.*²⁴ is meant polymyalgia rheumatica²⁵ and giant cell arteritis²⁶ for there is considerable evidence that both disorders are phases of the same disease, an inflammatory arteritis affecting both sexes past middle age. The arteritis is on the whole a benign affair compared with most of the other arteriopathies in rheumatology and tends to be self-limiting, subsiding usually in two to six years. Like rheumatoid arteritis and unlike polyarteritis nodosa, the kidneys are rarely affected. Hamrin *et al.*²⁷ followed up six cases of polymyalgia rheumatica to necropsy. Four showed giant cell arteritis in the aorta and its large branches; in one no arteritis was found at necropsy, where previously findings in a temporal artery biopsy specimen had been positive. The arteritis is therefore not confined to temporal or cranial vessels and has a highly variable and unpredictable distribution. Blindness due to disease of the central artery of the retina may be seen in both phases of the disease, polymyalgia rheumatica and giant cell arteritis.²⁸

TREATMENT

Though group 2 anti-inflammatory agents ease symptoms they do not prevent blindness, whereas full doses of corticosteroids invariably do. Prednisolone 10 mg or less daily will effectively control symptoms in most cases of polymyalgia rheumatica, but larger doses, 40 mg or more daily, are needed to be sure of preventing blindness.

Discussion

We have discussed the inflammatory pathological processes in four different arthropathies and seen how, by using much the same anti-inflammatory drugs, we modify these processes and ease symptoms in these different disorders. The nature of the inflammatory response is still imperfectly understood. Willkens and O'Brien,²⁹ in an excellent review of the non-steroidal anti-inflammatory agents, call it "an elaborate scheme of interacting events involving multiple chemical mediators, the reticulo-endothelial systems, the blood coagulation and complement cascades, newly recognised plasma proteins such as IgE and possibly new hormonal regulators such as prostaglandins."

As this scheme of events may be triggered off by many stimuli—injury, antigen-antibody complexes, infection, and deposition of crystals—antibiotics, antihistamines, antiserotonins, and immunosuppressive agents are all potentially anti-inflammatory agents in certain circumstances. As Shen *et al.*³⁰ point out, several possible mechanisms have been suggested in relation to the action of indomethacin—notably, uncoupling of oxidative phosphorylation, inhibition of mucopolysaccharide biosynthesis, inhibition of tissue proteases, stabilisation of cellular and lysosomal membranes, inhibition of platelet function, effect on leucocyte migration, and, now, prostaglandin synthetase inhibition.

There seems to be a general correlation of in-vitro prostaglandin synthetase inhibition with the anti-inflammatory and analgesic effect of aryl acids such as indomethacin and its analogues, phenylacetic acids, and saicylates at therapeutic levels, but in relation to the clinically more potent anti-inflammatory agents—the corticosteroids—and to the delayed action agents—penicillamine and chloroquine—prostaglandin synthetase inhibition does not seem to play a part. Much has been written on the immunological aspect of rheumatoid arthritis, and undoubtedly immune mechanisms play a considerable part, but what the initial antigen stimulus is remains a mystery. Immunosuppressive agents, such as cyclophosphamide and azathioprine exert a beneficial effect at the risk of immediate and delayed toxic effects. Whether they act by virtue of their immunosuppressive action seems doubtful; it might be more accurate to label them anti-inflammatory and cytotoxic substances. Turk³¹ notes that action is at two different levels: (a) directly and specifically on cell proliferation during the immune response, and (b) non-specifically on the inflammatory pheno-

mena produced by the immune reaction in the periphery. The whole subject is well reviewed by Urowitz.³²

Conclusions

What then in fact are we effecting in our use of anti-inflammatory agents in these four disorders? In gout and polymyalgia arteritica we are effectively and rapidly controlling symptoms due directly to the inflammatory changes of the disease until these changes spontaneously subside—in gout usually after a few days, in polymyalgia arteritica after several months or years. By reducing pain and stiffness in ankylosing spondylitis we are allowing a more normal use of spinal and girdle joints and are therefore helping to maintain mobility and normal function and reducing crippling by ankylosis. In rheumatoid arthritis we are mainly reducing symptoms, pain, stiffness, swelling, and disability and in some cases improving general health. But in this disorder our control is adequate only in the milder cases and the larger doses of corticosteroids necessary for effective control cannot be used.

In none of the four conditions do we switch off or alter the natural course of the disease permanently. Useful as these agents are they are not curative nor are they the final answer in any of these disorders, but by symptomatic control they make life much easier for many sufferers. As Bradford-Hill remarked, in assessment of therapeutic end results, statistically speaking, "stone dead" hath no peer. But symptomatic ease and relief of pain and stiffness, often over many years, does not necessarily show up readily or at all in current clinical assessment; statistical assessments of progress or end result do not usually reveal the quality of life lived over this period nor the symptomatic relief obtained throughout.

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