The most serious complication was deep infection, which occurred in seven instances (10.8 per cent.). Possible predisposing causes were previous hip surgery (2); open reduction of dislocated femoral prosthesis (2); corticosteroid therapy (2); previous superficial wound infection (1). The only satisfactory treatment for deep infection was removal of the prosthesis. Other complications included superficial wound infection and haematomata (6), deep vein thrombosis (7), transient sciatic nerve damage (2), and discomfort due to wire sutures (5).

In a doctors' assessment based on pain relief and flexion, 78 per cent. of results were classified as excellent or good. The patients themselves assessed 85 per cent. of operations as excellent or good.

Discussion

DR. H. HILL (Stoke Mandeville) You might be interested to know of our results with hip replacement in 26 rheumatoid patients. We had less trouble with both superficial and deep infections but a very much higher incidence of deep vein thrombosis. In particular, I should like to draw your attention to two patients who had excision arthroplasties which were later converted to total hip replacement. One developed a deep infection down to the bone, and the other had a deep venous thrombosis. Both had recurrent dislocation of the prosthesis needing surgical reduction, and one of these still has recurrent dislocation but manages to get it back herself.

DR. M. GUMPEL (London) What was the overall rate of infection for the orthopaedic teams concerned and for the operating theatres, please? What were the overall infection rates for those orthopaedic teams in operations not related to replacement arthroplasty and, similarly, what were the rates of infection for those operating theatres? This will enable us to compare the infection rates in replacement surgery with the degree of infection that you normally get in these theatres.

DR. HARRIS I am sorry, I cannot tell you the rate of infection of the theatres. Certainly in our series of total hip replacement for osteoarthritis, the rate of infection was appreciably lower, being about 5 per cent. (Todd, Lightowler, and Harris, 1972).

DR. B. M. ANSELL (Taplow) I was particularly interested in your comment on infection when a replacement is a secondary procedure. Our infection rate in Heatherwood/Wexham/Taplow is somewhat similar, and we have been particularly struck by the fact that, when total hip replacement follows a previous procedure, our infection rate is very much higher. This is a very important point to be borne in mind when considering surgery for rheumatoid subjects.

DR. HARRIS Mr. Charnley finds the same increased incidence when he does repeat operations at Wrightington (Dupont and Charnley, 1972).

DR. A. G. MOWAT (Oxford) I can partly answer Dr. Gumpel's question. In Oxford we have not found any significant difference in wound infection rates, either in total hip replacement or in other operations, between rheumatoid and non-rheumatoid subjects. Certainly the question of steroids has been examined carefully and does

not seem to be so important as has previously been suggested. The only correlation of problems of wound healing with steroids was on duration rather than dosage; there seems to be some effect only after 3 years. I should also like to mention that two of your deep infections occurred in patients who had been on steroids over 3 years. Do you regard this as a complication of the operation or as a pyarthrosis occurring in rheumatoid patients? It has been suggested that hospital patients have a 3 per cent. incidence per year of pyarthrosis (Karten, 1969).

DR. HARRIS Yes, I suppose it is possible that infection might have occurred if they had not had the total hip replacement. It would probably be unfair to say that the infection was unrelated to the operation if it occurred only in the operated joint.

DR. A. B. MYLES (Chertsey) The question of steroids and infection after operations is always coming up and is always spoken of as 'previous steroid therapy'. There is quite a lot of evidence to suggest that it is not *previous* steroid therapy but *current* steroid therapy, that is to say unnecessarily large corticosteroid cover for surgery, which is the most important factor (Winstone and Brooke, 1961).

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Penetration of Ampicillin and Cloxacillin into Synovial Fluid and the Significance of Protein Binding on Drug Distribution. By A. HOWELL, R. SUTHERLAND, and C. N. ROLINSON (*The Middlesex Hospital and Beecham Research Laboratories*)

Pyogenic arthritis may be caused by a wide variety of organisms, of which a penicillin resistant staphylococcus is one of the most common. It was felt to be of interest therefore, to study the passage of two semi-synthetic penicillins, ampicillin and cloxacillin, from the serum into the joint fluid. The drugs were given orally to patients with rheumatoid arthritis or osteoarthritis who had chronic joint effusions. Samples of serum and joint fluid were obtained at regular intervals after administration, and the levels of the antibiotics were measured. Both cloxacillin and ampicillin diffused readily across the synovial membrane. However, the levels of ampicillin in the joint fluid approximated quite closely to the serum levels whereas the synovial fluid concentrations of cloxacillin were much lower than those in the serum.

As cloxacillin is known to be much more highly bound to human serum protein than ampicillin, it was thought that this might account for the results. Further experiments were carried out in which the concentrations of free cloxacillin were estimated, having measured the degree of protein binding of the drug in each patient's serum and joint fluid by the ultra-filtration technique. There was a much greater similarity between the free levels of cloxacillin in the serum and synovial fluid than between the total levels. This suggests that protein binding has an

important effect on the movement of penicillins across the synovial membrane.

The levels of ampicillin and cloxacillin found in the synovial fluid exceeded the minimum inhibitory concentration for the majority of infecting organisms, with the exception of some of the Gram-negative bacteria.

Discussion

DR. L. E. GLYNN (*Taplow*) Were any of these patients on anti-inflammatory drugs; it has been suggested that most will displace protein-bound peptides and other protein-bound components (McArthur, Dawkins, and Smith, 1971).

DR. HOWELL We stopped all these patients' drugs 48 hours before each experiment so as to eliminate this factor. Three, however, were on steroids. Steroids are bound to protein, so this may have played a small part, but did not affect our results.

DR. J. A. MATHEWS (*London*) It is probably safe to assume that the appearance of drugs in the joints of your volunteers would be the same as in patients who actually have a septic arthritis. I am not quite clear, however, whether the activity of the drug is the same in the presence of pus. The implication of your paper is that it is safe to give these drugs orally, but I do not think this should confuse the question whether it is desirable to aspirate pus from a bacterially inflamed joint.

DR. HOWELL Yes, I agree with that, but just wish to make the point that antibiotics do get into the synovial fluid and that you probably do not need to give repeated intra-articular injections. Obviously, the higher the level in the synovial fluid the better.

PROF. E. G. L. BYWATERS (*Taplow*) Would it not be more relevant to the clinical situation if the effects of repeated doses were studied? I should have thought that these things always take some time to reach equilibrium and that the free and total levels would be very much higher with continuous dosage.

DR. HOWELL I do not know that that would be so. If you are giving these drugs 4- to 6-hrly, you presumably get a picture similar to ours, which will be repeated again and again over the 24-hr period. In a therapeutic situation, of course, I think you would want to give your drugs systemically so as to get high levels; I think you would be getting levels which go up and down and that at peak levels the situation would be comparable to what we have shown.

PROF. K. W. WALTON (*Birmingham*) Most of the curves you have shown were presumably mean curves, but all these patients had effusions and clearly there may well have been some differences in the degree of alteration of capillary permeability and therefore in the size of the protein molecules that could cross the synovial membrane. Antibiotics are bound to proteins that cross this barrier and I wonder to what extent you found differences depending on any other parameter which would allow you to assess the degree of change in permeability of the synovium.

DR. HOWELL We did not find very great differences between the patients with rheumatoid and osteoarthritis, who might be assumed to have different degrees of inflammation. Our point is that the free drug crosses the barrier very rapidly and that the protein-bound drug does not. With increasing inflammation, synovial fluid protein is indeed increased, but in practical terms you are actually concerned about the concentration of free drug. The protein-bound drug crosses the synovial membrane relatively slowly compared to free drug.

DR. B. VERNON-ROBERTS (*London*) Further to what Prof. Bywaters was asking in terms of repeated doses, is it possible to saturate protein binding so that repeated doses provide a higher free antibiotic level?

DR. HOWELL You can saturate the protein binding *in vitro* but not until an extremely high value in the order of over 100 $\mu\text{g./ml.}$ is reached. These levels are not obtained in the clinical situation.

DR. W. W. BUCHANAN (*Glasgow*) Deodhar, Russell, Dick, Nuki, and Buchanan (1972) in Glasgow, carried out similar studies with fusidic acid. After one dose they found a discrepancy between the serum and synovial fluid levels, but with repeated doses this disappeared. After 3 to 7 days the levels were equal.

DR. HOWELL This was presumably because protein-bound drug in the serum was reaching equilibrium with that in the joint fluid.

DR. A. J. PALFREY (*London*) May I sound another note of caution: these studies were done on joints with chronic effusions. Our viscosity studies on synovial fluid (Davies and Palfrey, 1968) suggested that the fluid present in a joint with a chronic effusion was very different from that in a normal joint. I do not know what the fluid is like in a joint with a bacterial infection.

DR. HOWELL I am not sure that I can answer that one.

SIR HENRY OSMOND-CLARKE (*London*) This is a very neat little paper, which I thoroughly enjoyed because it backs up my clinical experience in the use of ampicillin and cloxacillin, but I must emphasize that, if anyone is treating a swollen joint, there is no harm or distress in aspirating the joint to make sure whether there is pus or not, and subsequently draining the joint in addition to using antibiotics.

DR. HOWELL I am in complete agreement with that.

PROF. E. G. L. BYWATERS (*Taplow*) Perhaps I may add to my previous remarks about repeated dosage, that the protein-bound antibiotic presumably serves as a store rather like bound oxygen on haemoglobin. As free antibiotic diffuses out just as well as in, this store of bound antibiotic is obviously clinically useful when the serum level of free antibody falls, as it always will towards the end of the injection period.

DR. HOWELL Yes indeed.

DR. A. B. MYLES (*Chertsey*) We are talking of staphylococci, yet we do not normally treat staphylococci with ampicillin;

we usually use penicillin, and the choice of drugs is really between penicillin and cloxacillin. When we are dealing with a septic arthritis, we usually think it is due to staphylococci. Is there any information you can give us about the protein binding of penicillin G?

DR. HOWELL Benzyl penicillin is much less highly bound than cloxacillin. Obviously it would diffuse into the joint very much better and would be the best drug to use against a penicillin-sensitive staphylococcus.

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Studies on the Mode of Action of Non-Steroid Anti-Inflammatory Drugs. By D. A. WILLOUGHBY and M. DI ROSA (St. Bartholomew's Hospital Medical College)

We have previously shown that analysis of the carrageenin-induced oedema in the rat paw is produced by a sequential release of mediators (Di Rosa, Giroud, and Willoughby, 1971). This model of inflammation is widely used in the screening of new anti-inflammatory agents—at the time when the inflammation is usually assessed (3 to 4 hrs) this coincides with the release of prostaglandins.

The methods employed for producing oedema in the rat paw and its assessment were as previously described by Di Rosa and Willoughby (1971).

It was found that the inflammatory response from 2½ to 6 hrs after the injection of carrageenin, *i.e.* the prostaglandin-mediated phase, is closely associated with the migration of leucocytes into the inflamed area. The following non-steroid anti-inflammatory drugs: aspirin, indomethacin, mefenamic acid, and butazolidin, all inhibit the migration of monocytes from the inflamed

vessels. These agents also inhibit the phagocytic activity of these mononuclear cells.

It is concluded that these agents exert their activity on the carrageenin model of inflammation by inhibiting the migration of monocytes, which in turn are responsible for prostaglandin release. The main effect of these agents is on the surface of the leucocytes inhibiting mobility.

Discussion

DR. B. VERNON-ROBERTS (London) With more tissue oedema, cells are generally separated more widely. How have you assessed the relationship between oedema and the cell counts in sections? This is always a difficult problem.

PROF. WILLOUGHBY We have not found this so difficult. We do a large number of cell counts per section.

PROF. C. A. KEELE (London) Do you think that the migration of monocytes is responsible for the prostaglandin release, or alternatively do the prostaglandins cause the migration of monocytes?

PROF. WILLOUGHBY I think the hidden meaning in your question, if I am not mistaken, is 'Are the cells carrying with them enzymes as Vane (1971) described for synthesizing prostaglandins, or alternatively, do we believe that they are carrying preformed prostaglandins?'. I think the latter is the way the relationship really exists. We believe that initially the leucocytes are responsible for the prostaglandin release, although it has been shown by Kaley and Weiner (1971) that prostaglandin E_1 is chemotactic for leucocytes using *in vitro* methods. Possibly other factors initiate the migration of cells and this is then maintained by prostaglandin E_1 .

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