Conference report

Heavy metals and arthritis

The fourth annual day conference in the series ‘Growing Points in the Treatment of Arthritis’ was held at the Granby Hotel, Harrogate, on 7 April 1983. It was devoted to the topic ‘Heavy Metals and Arthritis’ and attracted an audience of about 100, both physicians and chemists. Professor Verna Wright and Dr Howard Bird acted as chairman.

Dr P. J. Sadler (Department of Chemistry, Birkbeck College, University of London) reviewed current knowledge of the chemistry of zinc, copper, and gold. Metals are far from the inert structures envisaged by some physicians. The reactivity of the metal or metallic ion is an amalgam of the charge present on the ion, the co-ordination geometry, and its mobility in biological systems. In addition, consideration had to be given to other elements such as the sulphur atom present in D-penicillamine and the potential for reduction or oxidation in the tissues. Metals in drugs were in equilibrium with metal-containing enzymes such as cytochrome oxidase (which contains copper), and these enzymes could exist in a variety of forms. The synthesis of metallothionines, present in all tissues, could be regulated by trace amounts of metal ions such as Ca**, Zn**, and Au*** and this in turn might explain the mode of action of metal containing drugs.

Copper and zinc

The remainder of the morning session considered copper and zinc. Dr D. Grennan (Manchester) complemented these theoretical considerations with a clinical evaluation of serum copper, zinc, and caeruloplasmin in patients with active rheumatoid arthritis, osteoarthritis, and in controls. Serum levels of copper and caeruloplasmin were significantly higher and zinc significantly lower in osteoarthritis than in controls. Copper and caeruloplasmin were still further raised in the rheumatoid group compared with the other 2 groups, and zinc was lowered in the rheumatoid group, though not more so than in osteoarthritis.

Dr J. S. Dixon, a biochemist (Harrogate), then compared the use of D-penicillamine, trien, and captopril in active rheumatoid arthritis. Penicillamine had been shown to be effective both in clinical terms and in biochemical terms as judged by a rising histidine and total serum sulphydryl and a falling plasma viscosity and C-reactive protein. Trien, a metal chelating drug that is used in an alternative to D-penicillamine in the treatment of Wilson’s disease but which does not contain an -SH group, was ineffective. By contrast captopril, an angiotensin-converting enzyme inhibitor with a structure similar to D-penicillamine (including an -SH group) caused improvement comparable to that from D-penicillamine. It was argued the mode of action of D-penicillamine was more likely to lie with its -SH group than with its metal chelating properties.

Dr A. J. Kennedy (Roche Products Ltd) discussed the use of the Lipsky-Ziff assay system for the study of in-vitro lymphocyte function from animals treated with D-penicillamine and other drugs. A variety of drugs that might have a penicillamine-like action had been studied in this system and some novel compounds that appeared effective were being considered for clinical trials. Many of these contained sulphhydryl groups. The intimate role of metals, including copper, in this system was stressed by the chemists.

Dr R. J. Ward and co-workers (Northwick Park Harrow) then discussed their serial estimations of copper and zinc in patients with rheumatoid arthritis being treated with second-line drugs. Patients had been treated with aurothiomalate, auranofin, D-penicillamine, or hydroxychloroquine. The raised plasma copper fell before a more gradual rise in the lowered plasma zinc as the patients came under chemical control. It was argued that even gold compounds were working through copper metabolism.

After a lunch break the afternoon programme moved from copper and zinc to a consideration of iron and gold.

Iron and gold

Iron-free radicals and rheumatoid synovitis were considered by Dr D. R. Blake (Birmingham). He argued, using in-vitro, in-vivo and animal model evidence, that iron might exacerbate rheumatoid arth-
ritis through the formation of the highly inflammatory hydroxyl radicals. In-vitro, ferrous iron, but not ferric, promoted hyaluronic acid degradation, and this reaction was inhibited by iron chelating drugs, OH' scavengers, and caeruloplasmin. In-vivo the ferroxidase activity of caeruloplasmin was significantly depressed in joints with rheumatoid synovitis, and in animals desferroxamine, an iron chelating agent, inhibited the chronic phase of some models of inflammation. A trial of desferroxamine in man might be of interest in confirming the hypothesis.

Brief clinical and immunological papers on gold compounds then followed. Dr J. Mackenzie (Peterborough) described her clinical success in the use of sodium aurothiomalate in a dose of only 10 mg weekly compared with the more conventional 50 mg weekly at the start of treatment. She argued that trials that used the conventional higher dose of aurothiomalate as a comparative product provided too high an incidence of side effects. Dr S. J. Hopkins (Manchester), an immunologist, described his work on lymphocyte activities in-vitro with gold sodium thiomalate. Various factors affected activity and kinetics in mouse lymphocytes, though the relevance of this test system to human rheumatoid synovitis was questioned by the audience.

Dr S. R. Rudge's study from Nottingham was based on the in-vivo dissociation of sodium aurothiomalate in rheumatoid arthritis. Radiolabelled work had suggested an early dissociation of injectable gold in the body into thiomalate and gold. An assay for free thiomalate had been developed and recovery rates after injection in patients with rheumatoid arthritis suggested that the thiol was freely available during early therapy, the gold less so. The possible contamination of commercially available sodium aurothiomalate with some free thiomalate and the implication of this for the results was discussed.

In an integrated presentation from Glasgow, a biochemist (Dr D. Brown) and a physician (Dr D. Lewis) evaluated redox parameters in patients receiving auranofin, aurothiomalate, or placebo. The choice of superoxide dismutase activity (SOD), plasma and lysate thiol (PSH and LSH) concentrations, and caeruloplasmin oxidase (CP) activity as assays that reflected both intra- and extracellular free radical activity was explained by Dr Brown. Dr Lewis had studied 90 patients with rheumatoid arthritis and classified them as 'responders' and 'nonresponders' in the 3 treatment groups. Responders showed an initial further deterioration in SOD and LSH levels followed by return to more normal levels. The PSH and CP did not show the same early change but returned to more normal levels after 24 weeks in the responders. 'Nonresponders' showed no such change. Gradual clinical improvement appeared to be preceded by an initial proinflammatory response.

In the final paper Dr R. J. Horton (Smith, Kline and French) outlined the comparative safety and efficacy of auranofin and parenteral gold compound, drawing on a large computer-based data bank from studies all over the world. Reference was also made to poster demonstrations by Keegan and Cole, who compared oral and injected gold in patients with rheumatoid arthritis, and Hunt and Holt whose poster described an open dose ranging study of auranofin in rheumatoid arthritis.

The next conference in the series will convene on 5 April 1984, and suggestions for topics, clinical or laboratory, would be welcomed by the organiser, Dr H. A. Bird.

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