

Brief communication

Effect of D(-)penicillamine on chronic experimental arthritis in rabbits

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SUMMARY Preliminary observations on the effect of D(-)penicillamine on chronic antigen-induced experimental arthritis in rabbits are reported. Daily oral administration of penicillamine, at a dose equivalent to that usually administered to rheumatoid arthritis patients, diminished the arthritis in 2 out of 3 animals as assessed by both measurement of joint circumference and histological examination.

Although D(-)penicillamine has been shown to be of therapeutic value in the treatment of rheumatoid arthritis (Multicentre Trial Group, 1973), its precise mode of action in this condition remains unclear. Unfortunately, any attempt to understand the basis of the clinical effects of penicillamine at the molecular or cellular level is complicated by the usual practice of its co-administration with known anti-inflammatory drugs such as corticosteroids and aspirin. This problem may be overcome by investigation of the influence of penicillamine on experimental models of arthritis in animals. However, previous studies (Liyanage and Currey, 1972) have shown that this drug failed to affect adjuvant arthritis in rats. We report now the findings from a preliminary investigation of the effects of penicillamine on the rabbit experimental arthritis model of Dumonde and Glynn (1962) where the compound was observed to bring about an impressive reduction in joint swelling in 2 out of 3 animals which survived the study.

Experimental arthritis was induced in New Zealand White/Californian cross rabbits, using ovalbumin as antigen, as described by Consden *et al.* (1971). The animals were immunized by two subcutaneous injections of ovalbumin in Freund's complete adjuvant, and challenged 6 weeks later by intra-articular injection of the antigen into the right knee (the left knee being injected with saline as a control), after the existence of delayed hypersensitivity to the antigen had been established by skin testing. Each rabbit produced an arthritic response in the antigen-

injected joint, which continued through an acute phase into a chronic phase. At this state (ie 115 days after intra-articular injection) there appeared to be some variation between animals in the degree of inflammation of the antigen-injected joint, as judged by increase in joint circumference (determined by tape measurement). Consequently, the animals were paired according to the circumference of the antigen-injected joint; one animal of each pair being treated with 60 mg D(-)penicillamine (Distamine™) per day; ie 15 mg per kg body weight, a dose equivalent to that usually received by human rheumatoid arthritis patients. The drug was administered orally in gelatin capsule form, by expulsion from a tube connected to the end of a syringe.

One animal failed to survive penicillamine treatment; of the 3 remaining animals receiving oral penicillamine, 2 appeared to respond to the drug after 4 and 8 weeks of treatment respectively as judged by a marked decrease in the circumference of the antigen-injected knee joint relative to the saline-injected (control) knee (Fig.). In contrast, no decrease in the degree of swelling of the antigen-injected knee joints of the control (ie no penicillamine) animals was observed. The experiment was continued until 325 days after intra-articular injection, when all the animals were sacrificed and the knee joints examined.

Post-mortem histological examination of the antigen-injected joints of the control (no penicillamine) animals showed considerable inflammation as judged by villous hyperplasia and infiltration of plasma cells and lymphocytes into the synovium.

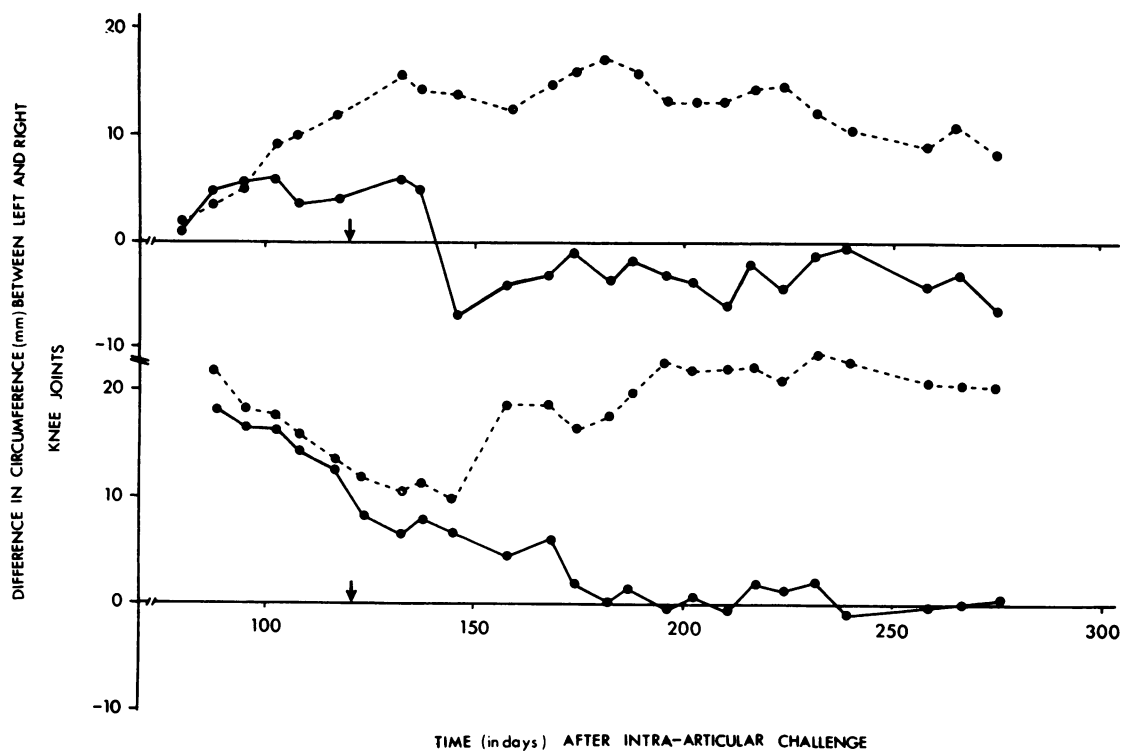


Fig. The difference in circumference between the antigen-injected (right) knee joint and saline-injected (left) knee joint are compared during the course of oral D(-)penicillamine treatment in two D(-)penicillamine treated (solid line) and two untreated control (broken line) rabbits. The vertical arrows indicate the beginning of oral administration of D(-)penicillamine.

Furthermore, severe erosion of articular cartilage and bone was apparent. In contrast, the antigen-injected joints of the 2 animals responding to penicillamine treatment showed a marked reduction in the degree of inflammation according to the same criteria, ie in both animals cellular infiltration into the synovium was drastically reduced and no synovial hyperplasia was apparent. However, considerable fibrosis was still present. One penicillamine-treated animal showed no erosive changes, whereas the other had only limited erosion of the articular cartilage. The remaining animal to which penicillamine had been administered showed no response to the drug as reflected by any of the previously mentioned criteria. However, post-mortem analysis showed that the antigen-injected joint of this animal was laterally dislocated and joint circumference measurements indicated that this may have occurred before administration of penicillamine. No evidence of inflammation could be found in any of the saline-injected knee joints.

Comment

In view of the recent claim (Goldberg *et al.*, 1974) that T cell-mediated immunity is of major importance in the rabbit experimental arthritis model, and that inhibition of this response results in a diminution of the arthritis, the results obtained in this study suggest that penicillamine might well be acting at the T cell level. Furthermore, Schumacher *et al.* (1975) have shown that pre-exposure of T cells to penicillamine *in vitro* resulted in a pronounced inhibition of the cellular immune response as measured by the mixed lymphocyte reaction; and Stanworth *et al.* (1976) have observed in rheumatoid arthritis patients starting oral penicillamine therapy an immediate rise in serum levels of IgE, the control of which is thought to be particularly T cell dependent. Although the results reported here are only of a preliminary nature and will now need confirming by tests on larger numbers of animals, they suggest that further use of the

Dumonde and Glynn (1962) experimental arthritis model might well help to elucidate the site and mode of action of penicillamine in rheumatoid arthritis; which, in turn, could have an important bearing on the ultimate understanding of the pathogenesis of this disease.

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