Commentary

Adjuvant arthritis 50 years on: the impact of the 1956 article by C. M. Pearson, ‘Development of arthritis, periarthritis and periostitis in rats given adjuvants’

M. W. Whitehouse

School of Medicine, Gold Coast campus and School of Biomolecular and Biomedical Sciences, Nathan campus, Griffith University, Queensland, Australia, P. O. Box 68, Stones Corner Qld. 4120, Australia, Fax: ++61 7 3349 3006, e-mail: whitehousemd@spin.net.au

Received 19 July 2006; returned for revision 16 October 2006; accepted by M. Parnham 19 October 2006

Summary. The Science Citation Index (Web of Science) has now accumulated over 700 citations to this report published in Proc Soc exp Biol Med 1956; 91: 95–101, including several in 2006. This memoire is a tribute to its author for revealing the opportunities for so much subsequent research in experimental pharmacology and toxicology.

For half a century, the adjuvant disease in rats has enormously aided research on drugs to control arthritis and other chronic inflammatory disorders. The adjuvant also triggers many systemic responses beyond the articular tissues. So we are given simultaneously a window to explore the converse phenomenon: namely, how a chronic disease can affect drug efficacy and toxicity. This phenomenon has been variously described as patho-pharmacodynamics, conditional pharmacology/toxicology and ‘a right nuisance!’ Nevertheless it has enormous heuristic value for clinical therapeutics.

Key words: Adjuvant arthritis – Collagen-induced arthritis – Conditional pathology/pharmacology/toxicology – Corticosteroids – Gold drugs

Introduction

Carl Pearson was an American physician with an abiding passion for understanding degenerative muscle diseases. Adjuvant arthritis was a happy accident, discovered by Carl soon after he joined the School of Medicine at the University of California in Los Angeles (UCLA). At that time he was searching for an animal model of polymyositis. It was known that rats and guinea pigs might be made auto-intolerant by injecting certain tissues homogenised with an immunostimulant such as the complete Freund’s adjuvant; this being a dispersion of dried mycobacteria (≤10 mg/ml) in a mixture of an emulsifier (15% v/v) with mineral oil (85% v/v). So Carl duly tried to set up an experimental model of allergic myositis by inoculating rats with muscle extracts emulsified with Freund’s adjuvant. Imagine his surprise on finding that the rats developed instead a form of chronic arthritis!

Carl’s genius then expressed itself in two ways. The first was simply to repeat the experiment but omitting the muscle extract – a rather obvious, but often neglected, type of control. The second was to painstakingly establish the unique pathology of the adjuvant-induced arthropathy. In this he was helped by Fae Wood, a most competent associate, with whom he was to publish several follow-up reports including the further seminal observation that cortisone injections suppressed arthritis development [1].

Only many years later was his research group able to report the successful establishment of an experimental myositis in rats enabled by collaboration in the late 60s with two very able visitors to UCLA, Graeme Morgan, a paediatrician from Sydney, Australia, and Brian Newbould, a pharmacologist from Macelesfield, UK [2].

Before this, Brian Newbould working in the ICI (now Astra Zeneca) Pharmaceutical Research Laboratories (Alderley Park, Cheshire, UK) had found that the adjuvant arthritis also responded to intramuscular injections of gold thiomalate (Myocrisin, Rhone-Poulenc) [3]. This too was something of a breakthrough for establishing that the gold therapies then being used for treating rheumatoid arthritis, could be validated in an animal model of chronic inflammation, allowing their anti-arthritic mechanism(s) to be investigated. (It is surprising how little has since been published about how gold drugs actually interact with the arthritigenic mechanisms in both this model disease and clinical arthritis. [4])
Subsequently not only ICI but most of the major pharmaceutical companies in Europe and North America quickly took up the hunt for new drugs to treat arthritis with the aid of the adjuvant arthritis assay. Even when quick assays, mainly based on suppressing acute paw oedemas, were preferred as the first test for recognising a new NSAID – ratification of their potential clinical value was soon sought from further screening in the adjuvant arthritis assay. This two-stage sequential approach had its drawbacks, failing to detect anti-arthritic agents such as corticosteroids and immunosuppressants that have little/no effect in the edema-suppression assays that primarily disclosed aspirin-like and prostanoid-suppressant drugs. Some pharmaceutical companies, notably ICI, persisted with the slower and more labour-intensive primary screening of drugs using the adjuvant arthritis; a two-week effort in contrast to the two-hour anti-oedema assay. They were rewarded with the discovery of exceptional drugs like Clozic [5] or Lobenzarit [6] without aspirin-like properties but proving to be anti-arthritic in subsequent clinical studies. A few anti-arthritic agents (DMARDs) such as chloroquine, dapsone and D-penicillamine had little impact on arthritis development in the rat but fortunately such instances were generally rare. Several reviewers have discussed the utility of the adjuvant arthritis from the ‘drug-hunters’ perspective [7–11].

The disease

But what exactly is the adjuvant-induced disease? Answers to this question range from the dismissive to the immensely complex. Carl’s first description of it in rats was that it was a periarticular arthritis and periostitis with all the hallmarks of chronic inflammation around, but not within, the joints. He noted the resemblance in its histological features to Reiter’s syndrome and involvement of the juxta-articular skeleton with initial osteoporosis and subsequent dysfunctional re-calcification of the joint, often causing articular fusion.

Many other tissue responses were involved, particularly adrenal hypertrophy and thymus involution, both reflecting a systemic stress reaction. These extra-articular responses justified calling the overall syndrome ‘adjuvant disease’ rather than ‘adjuvant arthritis’ to indicate that it was truly systemic involving many organs including the blood, bone marrow and liver.

The auto-immune character was first indicated by passive transfer of the disease from adjuvant-treated rats to syngenic rats with lymphocytes harvested from spleen or lymph nodes [12]. Removing a circulating lymphocyte population from pre-arthritic (adjuvantised) rats by draining the thoracic duct lymph not only provided a source of ‘pathophoric’ cells to transfer the disease but also arrested arthritis development within the donor rats [13]. It was then shown that removing thoracic duct lymphocytes from patients with rheumatoid arthritis induced remission of their disease within 14 days without medication [14]. As in the rat studies, this remission though impressive, was not permanent – indicating that the agent(s), provoking both the adjuvant disease in rats and rheumatoid arthritis in these patients, had not been inactivated but remained to eventually engender new populations of pathophoric lymphoid cells.

These parallel findings between experimental studies in rats and the UCLA clinic were significant at that time as they a) helped pinpoint circulating lymphocytes as effectors of a widespread chronic disease, not just transplantation crises; and b) established the relevance of the adjuvant disease as a tool for testing hypotheses about arthritigenesis in man. Until then (mid 1970’s) there had been much scepticism that the adjuvant disease had any relevance to human medicine since it could not be induced in other animals except a few hyper-reactive strains of mice. Fortunately many pragmatists working in the pharmaceutical industry continued to study the (un)natural history of this disease as they realised it provided remarkable opportunities to investigate the anti-arthritic effects of immunoregulant and anti-inflammatory drugs and hormones.

Further studies from Carl’s laboratories at UCLA established that the arthritigenic trigger lay in both the nature of the oil used to prepare the adjuvant [15] and the peptidoglycans present in the cell walls of gram positive bacteria [16]: this combination providing the requisite ‘immunostimulation’/adjuvanticity. Other investigators found an association with specific epitopes in the mycobacterial 65kDa heat-shock protein [17] but could not establish any cross reactivity with a cartilage-associated self antigen [18].

However very similar forms of arthritis could also be induced by eliminating the mycobacterial component altogether: for example, injecting rats instead with certain other oily immunostimulants e.g. pristane (C_{19}H_{40}) or squalene (C_{30}H_{50}) alone or by certain lipid amines dissolved in a carrier oil, e.g. avridine/CP-20961 [19] or DDA [20]; or even by incomplete Freund’s Adjuvant [21].

These additional findings suggested that the immunogen causing the arthritis might be endogenous i.e. a constituent of the rat or a viral protein or some combination of the two [19]. Since the arthritis could also be induced by direct micro-injection of Freund’s adjuvant [22], pristane or squalene (F. Beck & M. Whitehouse, unpublished), into surgically exposed inguinal nodes, this latent arthritigen may have already been present/trapped within these nodes. However, its ultimate provenance could still perhaps be exogenous e.g. an environmental toxin.

Why was this experimental disease so useful?

The answer surely lies in the fact that it was readily quantified. Without ‘pathometrics’ there could really be no ‘pharmacometrics’ and therefore any useful application of this experimental disease to drug discovery. Changes in rear paw size, or maximum tail thickness, are readily measured thereby providing non-invasive indices of disease onset and progression with or without the benefit of drug treatment. In some rat strains, and more notably males than females, reductions in body weight gain reflected first the initial recognition of the adjuvant and then continuing disease development. These simple objective physical measurements were a welcome contrast to monitoring other experimental models of chronic inflammation, e.g. granuloma responses or auto-allergy e.g. experimental thyroiditis. Here, evaluating the endpoints was much more subjective usually being