MND. Some may have been missed, or there may be unknown factors leading to clustering. As discussed in the paper, there are theoretical reasons why the association may be genuine, but the acid test will be the summated experience of departments of rheumatology and neurology elsewhere.

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Received 19 July 1989

The Ethics of Placebo Treatment in Rheumatoid Arthritis Drug Trials

Sir—In common with other rheumatologists I perform clinical trials involving NSAIDs. For some years, I thought in common with accepted practice, I have refused to undertake studies in rheumatoid arthritis which involve placebo periods. I was surprised recently not only to be asked to participate in a comparative study of two established NSAIDs which included pre- and mid-trial placebo periods, but also to be informed that I was unique in objecting to this practice.

I believe such placebo periods to be unethical. Their objective is to produce a flare in the patients’ symptoms, thus allowing the NSAID to demonstrate its effectiveness. This objective is occasionally justified by pseudoscientific statements regarding carry-over effects, but these effects can be readily accommodated without subjecting patients to harm. Are the patients harmed? As one of our major objectives is to benefit patients by relieving them of their symptoms, then we are, by definition, doing them harm by deliberately withholding symptomatic treatment. In addition, a small number of patients whose symptomatic control is good before having their medication withdrawn suffer a flare from which they do not rapidly recover—they are few, but we have all seen them.

We might claim justification of this small risk if our experiment were likely to give information of major importance, but we well know that comparative studies of NSAIDs will not give information of sufficient weight to justify even this level of risk to our patients.

The trial to which I have alluded claimed that it was to be performed in accordance with the Declaration of Helsinki (Vienna amendment), a copy of which was attached to the protocol. This clearly states: ‘In any medical study, every patient—including those of a control group if any—should be assured of the best proven diagnostic and therapeutic method’. All marketed NSAIDs have been demonstrated to be superior to placebo. The use of a placebo period cannot therefore be described as ‘the best proven therapeutic method’.

These trials are unethical. Their promoters provide documentation demonstrating they are unethical and we know they are unethical when we sign a protocol incorporating the Declaration of Helsinki. I contend that no such studies should be undertaken in the future and that those already started should be terminated immediately.

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Received 26 June 1989

Monoclonal Anti-cross-reactive Idiotyp Antibodies as Possible Probes for Lymphoproliferation in Primary Sjögren’s Syndrome

Sir—Primary Sjögren’s syndrome (1°SS) is a chronic systemic autoimmune disease associated with the production of a variety of autoantibodies including rheumatoid factors (RF) and characterized by lymphocytic infiltration and destruction of salivary and lacrimal glands. In addition to a marked polyclonal hypergammaglobulinaemia with the presence of autoantibodies [1], an increased incidence of monoclonal gammapathies [2, 3] and non-Hodgkin’s lymphoma (NHL) has been reported in these patients. The risk of lymphoma development is 44 times greater in SS than in the normal population [4], and 5–10% of these patients have been shown to progress to lymphoma [5]. Transition from autoimmune proliferation to malignant transformation may be a multistage process [5], in which a particular subpopulation of B-cell clones is selected. CD5+ B-cells appear to be candidates since they are involved in a number of lymphoproliferative disorders and are associated with the production of autoantibodies [6]. Thus, whilst only 10–20% of normal B-cells are CD5+, neoplastic B-cells in chronic lymphocytic leukaemia (B-CLL) are characteristically CD5+ and frequently express autoantibody specificities [7]. Similarly, paraproteins produced in patients with Waldenström’s macroglobulinaemia frequently express autoantigen specificities for DNA (30%) or IgG (10%) [8]. In patients with 1°SS, monoclonal B-cell proliferation takes place predominantly among RF-producing clones [9]. Increased expression of CD5+ B-cells has also been demonstrated in 1°SS [10, 11], and remission of malignant lymphoma in these patients was found to be closely associated with reduction of CD5+ B-cell clones [11]. It has recently been demonstrated that RF produced by unrelated individuals may be structurally similar and the products of inherited germ line genes. The structural similarities between these RF may be recognized serologically by the expression of common antigen markers referred to as cross-reactive idiotypes (CRI). Using monoclonal anti-CRI antibodies with specificity for monoclonal RF of the major wa idiotypic family, we have recently shown an increased expression of these CRI on RF from