The routine hæmatological and biochemical tests remained unchanged in both groups after treatment, and there were no local reactions to the injection of either agent.

Methotrexate is theoretically an attractive agent for intra-articular use in chronic synovitis since it would be expected to be active locally and is also safer than most other cytotoxic agents used in the treatment of inflammatory arthropathies. However, in this trial we have not found methotrexate used as a single 5 mg intra-articular injection along with 50 mg hydrocortisone to be superior to hydrocortisone alone, using objective tests of knee assessment under blind conditions. It must be stressed, however, that the patients included in this trial had active rheumatoid disease with long-standing synovitis of the knee complicated by secondary mechanical changes; the average erythrocyte-sedimentation rate in both groups exceeded 50 mm in the first hour, and knee radiography showed moderate destructive features. Maybe this type of patient is unlikely to respond permanently to any form of local medical treatment but they are a common and difficult therapeutic problem, since surgery is often also contraindicated.

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ACID-BASE DIAGRAMS

SIR,—Any student of acid-base balance would welcome innovations which make the teaching of acid-base principles and the management of acid-base disorders easier. Dr Grogono and his colleagues (Sept. 4, p. 499) claim that their acid-base diagram does just this. This design, however, needs closer analysis before uncritical acceptance.

Grogono et al. claim that their method avoids the concept of "base excess". Yet they introduce the term "metabolic acidosis" and allow a minus or negative form of this. Moreover, their values are remarkably close to base excess derived from a diagram in a paper[1] they criticise for having used in-vitro behaviour of blood to represent in-vivo disturbances.

If you take the data obtained by Albert et al.[2] in 60 patients with uncomplicated and untreated metabolic acidosis and subtract any observed HCO_3^- concentration from an arbitrary normal of 25 mmol/l, you get values within 1 or 2 mmol/l of the "metabolic acidosis" values obtained from the new chart. Similarly, from data on chronic respiratory acidosis in man,[3] the 95% confidence band for P_{CO_2} of 70 mm Hg encompasses a pH range of 7·28–7·40 and $[HCO_3^-]$ of 33–44 mmol/l. Simply subtracting $[HCO_3^-]$ from 25, gives values strikingly close to the "metabolic acidosis" values of −6 and −18, respectively, from the new diagram. Where lies the advantage of this method over knowing that, to correct acid-base abnormalities, P_{CO_2} should tend toward 40 mm Hg, $[HCO_3^-]$ toward 25 mmol/l, and pH toward 7·4, and that the degree of metabolic acidosis may be estimated by subtracting observed $[HCO_3^-]$ from 25? In either approach one still needs a careful analysis of patient history and clinical findings to work out how he arrived at his state of disorder and guide his return to normal, principles succinctly set forth by Schwartz and Relman many years ago.[4]

The data of Garella et al.[6] suggest that the 0·3 × body-weight formula for calculating HCO_3 replacement therapy, as used by the Syracuse workers, may at times greatly underestimate the actual amount required, but their cautious approach is probably generally warranted.

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IMMUNISING AGAINST RECEPTORS FOR ANTIGEN

SIR,—In your editorial (Sept. 4, p. 505) you review the subject of anti-idiotypic antibodies and the role they play in immune regulation and control with particular reference to transplantation immunology and autoimmunity. Another aspect is the appearance of similar anti-receptor-site or anti-idiotypic antibodies in malignancy.

You emphasise the importance of producing anti-idiotypic antibodies and their mechanism in suppressing immune reactivity against the particular antigen to which the idiotype was directed. We have found auto anti-idiotypic antibodies in the sera of patients with malignant melanoma, and have offered this as an explanation for the elimination of a particular anti-melanoma antibody.[1] Similar anti-antibodies have been demonstrated in animal models,[2] particularly the myeloma-lymphoma group. For instance, antisera produced against monoclonal IgM on the surface of a spontaneous lymphoma in NZB/NZW F_1 mice could confer protective immunity against the neoplasm.[3] In addition antibody against the antigen receptor in plasmacytoma of Balb/c mice prolongs the survival of these animals.[4]

Further evidence indicates that auto anti-idiotypic antibodies did occur,[5] and a dual role, in both suppression and activation of specific immune responses, has been suggested.[6]

We have demonstrated anti-antibodies against tumour-specific antibodies in the serum not only in melanoma but also in unrelated human malignancies,[7] especially in patients with prostatic carcinoma after cryosurgery.[8] The antibody directed against the prostatic carcinoma was transient, and we find that immunoglobulin in the negative sera from these patients specifically reacts with the tumour-antibody-positive sera, taken at a different time. The role of such anti-idiotypic antibodies is fundamental to the process of immune regulation.[9,10]

The events seen in autoimmunity, chronic parasitic infections, and malignancy are, therefore, likely to be reflections of derangement in immune regulation,[11] and the presence of anti-idiotypic antibodies may be potentially important not only in therapy, as suggested in your editorial, but also as a means of indicating failure of immune control.[12] The role of immune complexes composed of tumour antigens and anti-tumour antibodies in malignancy has received much attention. The possibility, however, that anti-antibody complexes might occur and be of some importance has been suggested, and demonstrated in our laboratories.[12] The importance of this in malignancy is considerable, both for prognosis and for immunotherapy, the reverse of the situation pertaining to transplantation. The fact that auto anti-idiotypic antibodies can occur makes therapy more feasible than you suggest because complex procedures and Freund's adjuvant would not necessarily be needed. It is important to realise that these mechanisms may strongly link together approaches to the studies of transplantation, autoimmunity, and malignancy.

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