On the ineffectiveness of indomethacin against rheumatoid swelling

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Previously, it was suggested that indomethacin-like drugs fail to arrest rheumatoid swelling because of their inability to prevent the inflammatory changes initiated by circulating sensitized lymphocytes (Jasani, 1975). The effectiveness of indomethacin against lymphocyte-initiated swelling and the accumulation of fibrin has been tested using the skin graft model (Bach & Jasani, 1976) and compared with that of two cortisol-like steroids: fluocinolone acetonide and chlorflumethasone.

To secure the development of circulating sensitized lymphocytes in the test animal, six homografts were transplanted on to each hind limb of the recipient rabbit and the drug was applied topically to one set only (Jasani, Parsons, Roberts & Tweed, 1974). The placebo-treated contralateral set provided the antigenic stimulus leading to the emergence of circulating sensitized lymphocytes (Jasani, 1976).

The results showed that indomethacin (0.02%) was virtually ineffective against the swelling in homografts; a failure which cannot be due to lack of absorption of topically applied indomethacin, which is known to be as active topically as when administered orally (Lewis, 1976). In contrast, the two steroids were definitely effective against both the inflammatory accompaniments. Compared with indomethacin which reduced the swelling only slightly ($96.6 \pm 0.9\%$) and tended to increase fibrin accumulation ($110.6 \pm 4.7\%$), fluocinolone acetonide (0.0025%) reduced the swelling and fibrin content to $66.2 \pm 6.3\%$ and $53.6 \pm 6.0\%$ respectively of control, whereas chlorflumethasone (0.00025%) reduced them to $62.2 \pm 5.1\%$ and $69.2 \pm 1.9\%$ (mean $\pm$ s.e. mean, $n = 4$).

As the accumulation of fibrin occurs in the rheumatoid joint in a manner similar to that in homografts (Bullock, Jasani & Roberts, 1976), the observations suggest that new anti-rheumatic agents should also exhibit steroid-like properties in their ability to depress lymphocyte-initiated inflammation but should be devoid of undesirable effects.

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Site of action of the antiallergic drugs cromoglycate and doxantrazole

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The degree of antigen-induced histamine secretion from sensitized mast cells is correlated with 45-calcium uptake (Foreman, Hallett & Mongar, 1975). Inhibition of oxidative and glycolytic metabolism prevents histamine secretion but not ^{45}Ca uptake, whereas dibutyryl cyclic AMP inhibits both ^{45}Ca uptake and secretion. Histamine secretion induced by the calcium ionophore, A23187 is not inhibited by dibutyryl cyclic AMP or by antiallergic drugs (Foreman, Mongar, Gomperts & Garland, 1975) indicating that these inhibitors exert their effect on antigen-induced secretion at the level of calcium entry into the mast cell.

The methods of measuring histamine secretion from, and ^{45}Ca uptake by sensitized rat peritoneal mast cells have already been described (Foreman, Mongar & Gomperts, 1973).

Cromoglycate and doxantrazole produce a dose-related inhibition of antigen-stimulated ^{45}Ca uptake by the mast cells. The concentration ranges for inhibition of ^{45}Ca uptake are similar to those for inhibition of histamine secretion (Garland & Mongar, 1976). Inhibition of ^{45}Ca uptake by dibutyryl cyclic AMP is