A new approach for studying the anti-rheumatic activity of indomethacin using the homograft reaction as a model for chronic immunologically-mediated inflammation

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Previously it was shown that during the homograft reaction there was an increase in the dry weight, DNA, and moisture content of rabbit skin homografts (Bitterli & Jasani, 1972). However, when the infiltration of lymphocytic mononuclear cells is maximally suppressed and the rejection delayed using cyclophosphamide there is no increase in these parameters above the values found in autografts transplanted onto similar anatomical sites in the opposite leg of the same animal (Jasani, 1973a).

In the present experiments the action of indomethacin has been compared with that of a glucocorticoid, fluocinolone acetonide, on the development of the homograft reaction.

Although equimolar concentrations of both drugs when applied topically at 24 h intervals reduced oedema formation as well as the infiltration of lymphocytic cells, the fresh weight of homografts of similar size receiving indomethacin *increased* whereas that of the glucocorticoid-treated homografts *decreased* significantly in comparison with control, non-treated homografts. Neither treatment delayed the onset of rejection by more than 24 h, i.e. rejection was only partially modified.

When dry weight and moisture content were measured separately it was found that indomethacin augmented by almost two-fold the increase in tissue dry weight whereas the glucocorticoid reduced it. On the other hand, both drugs reduced the increase in water content, fluocinolone acetonide significantly more than indomethacin.

Application of indomethacin to skin autografts resulted in a small though definite reduction of the normally occurring increase in their fresh weight. This was due mainly to diminished moisture content. In this respect indomethacin resembled fluocinolone acetonide, which, however, reduced also the dry weight of the autografts.

Tissue dry weight, when estimated as the acid-insoluble, lipid-free residue as recommended by Schneider (1945), represents mainly the amount of protein constituents of the skin. Since indomethacin does not influence it in the autograft, whereas fluocinolone suppresses it in the homograft in parallel with a significantly greater suppression of lymphocytic infiltration, it has to be concluded that the observed increase in dry weight of indomethacin-treated homografts may be related to some modification of a normal lymphocyte-mediated accompaniment; e.g. fibrin deposition (Colvin, Johnson, Mihm & Dvorak, 1973).

In addition, in homogenates prepared according to Jasani (1973b) indomethacin-treated homografts showed a significant increase in the sedimentable rather than the water-soluble portion of tissue constituents. The possibility that cell debris including nucleoproteins may account for the increase was excluded as indomethacin lowered the DNA of homografts by 30% of control, and collagen was excluded since the effect did not occur in autografts in which the connective tissue changes are more pronounced than in the homografts.

If the suggestion were confirmed, elucidation of the mechanism influencing the fibrin content of homografts may provide an insight into why the available indomethacin-like anti-rheumatic drugs, although allowing relief from joint pain and stiffness, do not arrest the development of the morphological accompaniments of rheumatoid arthritis such as synovial hypertrophy and erosive articular damage (Jasani & Buchanan, 1968).

References

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