The usefulness of homologous pairs of rabbit skin grafts for studying the pharmacology of anti-rheumatic agents

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It is possible to quantitate the absolute increase in the various tissue accompaniments of the rejection process in each individual homograft (Jasani, 1973a).

Furthermore there is no statistically significant difference between the dry weight, moisture content and DNA of homologous pairs of homografts, i.e. grafts transplanted onto identical anatomical sites on the opposite legs of the same recipient (Bitterli & Jasani, 1972). Therefore the influence of pharmacological agents can be examined in two ways.

The influence of a systemically administered compound, such as the immunosuppressive agent cyclophosphamide, may be studied by comparing the behaviour of homografts with that of autografts transplanted onto a homologous site (Jasani, 1973b). Data were presented to show that the method provides reliable information using single animals.

Alternatively, the influence of an anti-inflammatory compound may be assessed by applying it topically.

In the present experiments involving Norfolk rabbits, six homologous pairs of homografts, made using skin dissected from New Zealand white donors, were employed to compare the influence of three non-steroidal agents: acetylsalicyclic acid, phenylbutazone and indomethacin, with that of fluocinolone acetonide. Each was applied topically at 24 h intervals to one member of each homologous pair, 1 mg ointment containing equimolar concentrations (range, 2 to 200 nmol) being used per mg dry weight of skin grafted. The contralateral graft received an equivalent amount of placebo, i.e. the ointment base only.

Details of the operative and analytical procedures employed were illustrated and the removal of a homologous pair of grafts from a typical example for each type of drug was demonstrated.

Unlike one of the most widely used methods at present, namely the arthritis induced in rats by mycobacterial adjuvant (Newbould, 1963), the new approach has revealed qualitative differences not only between the steroidal and non-steroidal agents (Jasani, Lewis & Tweed, 1974) but also amongst the non-steroidal agents themselves.

For instance, phenylbutazone, like indomethacin, augments the normally occurring lymphocyte-mediated increase in the dry weight of homografts, whilst acetylsalicylic acid suppresses it slightly. Even more strikingly, only acetylsalicylic acid resembles the glucocorticoid in suppressing the normally occurring lymphocyte-dependent increase in the moisture content of homografts.

On the other hand, in a similar study using skin autografts which undergo healing without the intervention of lymphocytic cells, all the three agents suppress not only the increase in dry weight but moisture content as well, though in each case to a significantly lesser extent than the glucocorticoid.

The findings may have considerable relevance to the persistence of certain manifestations of rheumatoid inflammation, e.g. synovial hypertrophy, in spite of continued treatment: especially, in view of recent evidence which suggests that they may also be related to the biological activity of sensitized lymphocytes (Ishikawa, Andreis, Stastny & Ziff, 1973; Paulus, Machleder, Peter, Goldberg, Levy & Pearson, 1973; and Stastny, Rosenthal, Andreis & Ziff, 1973).

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