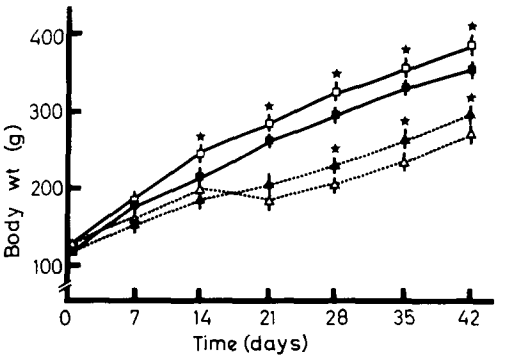

FIG. 2. Mean (± s.e.m.) body weight of non-arthritic control rats (——) and rats with AIP (- - - -) housed 1 per cage (□ △) or 10 per cage (■ ▲). n = 10 for each point. *$P < 0.05$ for comparison of each housing condition.

more pronounced in rats housed one per cage and remained so. This closely parallels the increased severity of AIP on paw volumes (Fig. 1) in similarly housed rats. By day 14 body weights of control rats were significantly higher for those housed one per cage and remained higher throughout the experiment, although the rate of gain (or slope of the body weight curve) was similar for both control groups.

The results of this experiment demonstrate that overcrowding affects the development of AIP in rats. Oedema formation for both the primary and secondary lesions of the disease and the severity of the reduction in body weight gain were less in rats housed ten rather than one per cage (of equal dimensions). In our laboratories, AIP studies are normally conducted as described above with the exception that rats are individually housed in cages affording approximately one-half the space (20·0 cm wide × 18·0 cm high × 25·0 cm long) allowed in the present study with disease development closely approximating that seen in the uncrowded rats (unpublished data).

May 28, 1980

REFERENCES

Maickel, R. P., Westerman, E. O., Brodie, B. B. (1961) J. Pharmacol. Exp. Ther. 134: 167–175

Newbould, B. B. (1963) Br. J. Pharmacol. Chemother. 21: 127–136

Selye, H. J. (1946) J. Clin. Endocrinol. Metab. 6: 117–230

Selye, H. J. (1950) The Physiology and Pathology of Exposure to Stress, Medical Publishers, Montreal, Canada, pp 52–70

Sofia, R. D., Knobloch, L. C., Vassar, H. B. (1975) J. Pharmacol. Exp. Ther. 193: 918–931

Swingle, K. F. (1974) in: Scherrer, R. A., Whitehouse, M. W. (eds) Anti-inflammatory Agents Chemistry and Pharmacology. Vol. II Academic Press, New York, pp 33–122

LETTERS TO THE EDITOR

Analgesic action of indomethacin in rats with trypsin-induced hyperalgesia

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Vinegar et al (1976) expressed the view that some non-steroid anti-inflammatory drugs possess analgesic properties only as a consequence of the inhibition of inflammation, while others are analgesic independently of their anti-inflammatory effect, and that the two classes could be distinguished from each other by their actions on hyperalgesia induced by injection of kaolin or trypsin into the rat's paw. Only those agents possessing independent analgesic properties were said to be active in these cases, and indomethacin lacked an analgesic component independent of anti-inflammatory activity, even at the very high dose of 5 mg kg^{-1}.

If this concept is valid, it has important implications for studies on the mechanism of action of these drugs and in the search for new and improved agents. We have, therefore, made additional observations, even though Van Arman et al (1968) had demonstrated block of trypsin hyperalgesia by indomethacin.

Trypsin (Sigma Chemical Co.), 1 mg in 0·1 ml, was injected into the right hindpaw of Sprague-Dawley female rats of about 50 to 60 g. The volume of each injected paw was determined immediately after injection, and both paw volume and threshold of response to pressure were measured at various times thereafter by methods previously described (Winter et al 1963; Winter & Flataker 1965). Indomethacin was suspended in 0·5% methylcellulose in a concentration to permit administration of 2 mg kg^{-1} in a volume of 1 ml/100 g body weight. Animals not receiving drug were given methylcellulose only.

Trypsin injection induced prompt development of oedema accompanied by hyperalgesia (Fig. 1). Indomethacin did not inhibit the oedema induced by trypsin, but it was highly effective against trypsin-induced hyperalgesia, and was equally effective whether given before injection of trypsin or if treatment was delayed until after hyperalgesia was established. Comparable results have been reported for diflunisal (Winter et al 1979).

It is clear that an analgesic effect can be obtained with these compounds independently of an antiinflammatory

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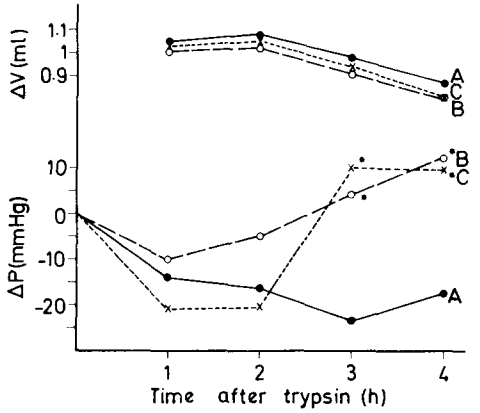

FIG. 1. Effect of indomethacin, 2 mg kg^{-1} orally, on oedema and hyperalgesia induced by injection of trypsin, 1 mg, in the rat hindpaw. Upper curves, ΔV = increase in foot volume; lower curves, ΔP = change in pain threshold after trypsin injection. A = controls, vehicle only, B = indomethacin 1 h before trypsin, C = indomethacin 1 h after trypsin, 10 animals per group. Significant ($P < 0.05$) differences, drug-treated vs controls, indicated by *.

action as judged by absence of inhibition of oedema volume. Our data do not support the hypothesis that non-steroid anti-inflammatory agents can be classified on the basis of an alledged lack of action upon trypsin-induced hyperalgesia.

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REFERENCES

Van Arman, C. G., Nuss, G. W., Winter, C. A., Flataker, L. (1968) in: Rocha e Silva, M. (ed.) Pharmacology of Pain. Proceedings 3rd International Pharmacological Congress, 1966, Pergamon Press, Oxford and New York, pp 25–32

Vinegar, R., Truax, J. F., Selph, J. L. (1976) Eur. J. Pharmacol. 37: 23–30

Winter, C. A., Risley, E. A., Nuss, G. W. (1963) J. Pharm. Exp. Ther. 141: 369–376

Winter, C. A., Flataker, L. (1965) Ibid. 150: 165–171

Winter, C. A., Kling, P. J., Tanabe, K. (1979) in: Weissmann et al (eds) Advances in Inflammation Research. Raven Press, New York, pp 527–534

Serum sulphydryl concentrations and antirheumatic drugs in rheumatoid patients

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A question has been proposed by Pickup et al (1980) on the reliability of the serum sulphydryl (SH) concentrations in monitoring the changes induced by long-term clinical trials in patients with rheumatoid arthritis (RA), and these authors have criticized Hall & Gillan's suggestion (1979) that stimulation of sulphydryl-disulphide exchange reactions in vivo may distinguish 'specific antirheumatic' drugs from non-steroidal anti-inflammatory drugs (NSAID's) in the treatment of RA.

Clinical assessment of disease activity and treatment-related changes in RA is an old and difficult problem. In attempt to by-pass it we have always associated determination of proximal interphalangeal joints technetium index (Tc-index), erythrocyte sedimentation rate (ESR), and joint count to measurement of serum protein SH concentrations in monitoring long-term treatment-induced changes in RA patients. Serum SH concentrations were measured spectrophotometrically using 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) by the original Ellman method (1959). We found that serum total SH concentration was significantly lower in 26 untreated RA patients, 17 females and 9 males, mean age 47 years (range 25 to 75), with classical or definite active RA (ARA criteria), than in age and sex matched normal subjects (mean values in RA patients, 246 s.d. 56, and in control subjects, 342 s.d. 49, $P < 0.001$).

A six month treatment with haloperidol significantly increased SH serum concentrations in all 12 treated patients, and significantly decreased Tc-index, ESR, and joint count (Grimaldi 1980a). The effects of haloperidol treatment on ESR, Tc-index as well as clinical parameters have been previously compared with indomethacin treatment (Grimaldi & Bergonzi 1980). Cyclophosphamide also has been shown to be able to significantly raise serum SH concentrations in RA patients after six months treatment and to induce a significant decrease in the Tc-index, ESR, and joint count (Grimaldi 1980b). No NSAID's were added to either haloperidol or cyclophosphamide treatment.

We believe that serum SH concentration might be used for objective measurement of disease activity and in monitoring long-acting antirheumatic drugs, along with radioisotope indices, acute phase reactants, and clinical parameters, since each method is measuring different component of the specific rheumatoid process.

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REFERENCES

Ellman, G. (1959) Arch. Biochem. Biophys. 82: 70–77

Grimaldi, M. G. (1980a) Scand. J. Rheumatol. in the press

Grimaldi, M. G. (1980b) Ibid. in the press

Grimaldi, M. G., Bergonzi, M. (1980) Curr. Ther. Res. 27: 565–575

Hall, N. D., Gillan, A. H. (1979) J. Pharm. Pharmacol. 31: 676–680

Pickup, M. E., Dixon, J. S., Bird, H. A. (1980) Ibid. 32: 301–302