Correspondence

Sir,

Walker and others (1975) conclude that, 'Our findings do not support those of Stevenson and others (1971) in that there is no significant increase in chromosomal damage in lymphocytes of patients exposed to phenylbutazone (PBZ) or oxyphenbutazone (OPB)'.

They express their findings in terms of unstable (Cu) and stable (Cs) chromosomes, but in the following comments only the latter (dicentric and ring chromosomes) will be considered. The Liverpool authors include even chromatid gaps and breaks in their Cu scores and these could not have arisen *in vivo*. They report on findings in lymphocytes of 44 patients with rheumatoid arthritis currently taking PBZ or OPB, and for brevity they will both be called PBZ. The durations of treatment are not stated. In 4178 metaphases from the patients they found 8 dicentric or rings (D+R) or 0.19%. They had 44 'controls' with rheumatoid arthritis matched for age and sex with the patients under treatment. Of these 19 were not known ever to have had PBZ and they had 3 D+R in 1900 cells (0.16%). This is a high frequency for D+R in the population and compares with 0.06% in the Oxford control subjects. However, the sampling errors of the proportions are obviously very large.

The remaining 25 controls were patients who had had at varying times, up to 12 months before test, courses of PBZ. In this group they found 9 R+D in 2500 metaphases (0.36%). It is difficult to see why these 25 patients were classed as 'controls' and not as treated patients. If trying to test the hypothesis which was suggested by the Oxford data that PBZ induces damage to lymphocytes *in vivo* in the G₀/G₁ stage of the cell cycle then it has to be remembered that the frequency of rings and dicentric induced *in vivo* only falls by about 50% in three years as those cells, which have difficulty in giving rise to viable daughter cells, so seldom divide *in vivo* (Norman and others, 1965, Buckton and others, 1967). As judged by Table III in the paper of Walker and others, the mean time after taking PBZ for the 25 controls was about 4 years. It follows that in testing the hypothesis that PBZ does induce damage, the figure of 0.36% of cells having R+D has to be regarded as a minimal estimate of the previous level, when these patients had first completed their courses, and it can be estimated that the level then was more than twice as high.

The level in treated patients in the Oxford series was 27 R+D in 4928 metaphases (0.55%). As duration of treatment of those continuing under treatment in Liverpool is not given it is not possible to make a comparison with those from Oxford, but Table III in the Liverpool paper suggests that no 'controls' were under treatment for more than one year while the mean duration of treatment of patients studied in Oxford was 32 months.

Bearing in mind the low frequencies of all R+D damage and the consequent large confidence limits of estimates it is not surprising that there should be differences in findings in parallel investigations. In this instance, however, when the Liverpool and Oxford data are compared it is likely that there is very little real difference in the findings. The findings of R+D frequencies in the 44 subjects under treatment plus twice these in the 'controls' treated in the

past would be about 0.39%, which is not very different from the Oxford figure of 0.55%.

In short it could be argued that rather than 'do not support', the Liverpool data are really 'not incompatible with' the Oxford data. That is not to argue strongly that the Oxford data reflect the true picture, but in view of the points made above it can be argued that they are more likely to do so than those from Liverpool.

It is perhaps of interest to make two further points. In 100 cells from each of 12 patients who had taken oxyphenbutazone for at least three months one of us (A.C.S.) found no dicentric chromosomes, which suggests that OPB is not the metabolite of PBZ which damages chromosomes. This is against our argument to some extent in that three of the eight dicentric chromosomes found in the patients under treatment in Liverpool were in patients taking OPB, whereas only one of the nine dicentric in treated 'controls' came from patients who had previously taken OPB only.

The second point arises from a study undertaken by Dr. R. L. Lindernbaum in Oxford, to whom we are indebted for permission to quote his findings. In the course of a study of 32 individuals over 22 years of age who had been under treatment for congenital dislocation of the hip since infancy Dr. Lindernbaum took blood samples primarily to see whether there was any evidence that the very large number of diagnostic x-ray examinations resulted in recognizable chromosome damage. No such evidence was found.

In 3138 metaphases from lymphocytes of these patients 7 (0.22%) had dicentric. However, Dr. Lindernbaum had noted the history of drugs taken by these 32 patients and on further analysis it was found that exactly half had taken PBZ. In those who had taken PBZ 5/1583 (0.32%) of cells had R+D, and in the remainder 2/1600 (0.13%) had R+D. Again although not significant this finding points in the same direction as the Oxford and Liverpool findings, and those of Stevenson and others (1972) in horses given phenylbutazone.

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