vertebral joints is readily found. I have a macerated specimen of a rheumatoid spine in which every costovertebral joint shows naked eye erosive change. Indeed the costovertebral joints, that is to say the facets on the vertebral body, are more severely involved than the corresponding posterior zygapophyseal joints, and I wonder whether this kind of differential has been found by Prof. Bywaters? However, in the thoracic spine all the lesions I have encountered have been restricted in terms of their erosion of the vertebral bodies, that is, the erosion does not spread around as it does in the cervical spine. Now, just to comment about the lumbar lesions. In the original cases reported by us which were subject to histological study, I found no evidence that any of the lesions in the lumbar spine could be attributed to what I would recognize as a rheumatoid process: all of them were explicable in terms of disc and end-plate failure, porotic collapse, or pyrogenic inflammation. The first slides shown by Prof. Bywaters of the lumbar spine show lesions which one can find quite readily in nonrheumatoid lumbar spines and I think we should be very careful about interpreting tissue damage in the rheumatoid as always being of rheumatoid origin.

PROF. BYWATERS Involvement of apophyseal joints, I agree, may be slightly less frequent. The thoracic costovertebral lesion does not involve the whole of the disc as I have already shown in a number of areas: I think this is possibly because of the more restricted movement there is in the thoracic spine as compared with the cervical spine or even the lumbar spine. In the cervical spine there can be complete loss of disc substance and complete loss of all cartilage on the apophyseal joints. The lumbar spine lesions are always very difficult to interpret. I raised with the Society some years ago when was a pile a rheumatoid pile, and I think the same question may be being raised in relation to the lumbar disc lesion. I thought they were rheumatoid because they showed inflammatory characteristics and reactive sclerosis. These spinal lesions do not show the characteristic plasma cell and lymphocyte deposits which you see in peripheral joints and they are always more difficult to interpret, but I thought they were rheumatoid lesions. One does not see uncomplicated disc degeneration with collapse, and this bony sclerosis which is a characteristic sign of an inflammatory response.

DR. J. BALL (Manchester) It is important to recognize that a little inflammatory infiltration associated with loss of haemopoietic tissue will occur in the vicinity of traumatic lesions in vertebral bone. It is just because this can happen in a clearly nonrheumatoid state that you have to be really careful about putting too much emphasis on a few lymphocytes and plasma cells.

DR. R. J. FRANCOIS (Brussels and Louvain) I congratulate Prof. Bywaters for his very interesting data. About the patient, whose microscopical sections were shown, I would like to know for how long he had been suffering from the thoracic spine, and if the involved discs showed any development of syndesmophytes?

PROF. BYWATERS No syndesmophytes! The duration of the clinical lesion was very difficult to determine. The lady who had had rheumatoid arthritis for some 30 years was in a very decrepit state and complained of pain all over for many years.

DR. F. DUDLEY HART (London) Did she have restriction of chest and thoracic spinal movement?

PROF. BYWATERS There was general restriction of movement during the last years of her life. I was unable to show any particular thoracic lesions, though the x-ray did show these, and I imagine she did have limitation.

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Metabolic Studies of Thiopurinol in Man and Pig. By R. GRAHAME, H. A. SIMMONDS, A. CADENHEAD, and B. M. DEAN (Departments of Rheumatology and Medicine, Guy's Hospital, and Professional Medical Unit, St. Bartholomew's Hospital, London; Rowett Research Institute Aberdeen)

Thiopurinol (mercapto-4-pyrazolo (3,4-d) pyrimidine) has been shown in two French studies (Delbarre, Auscher, de Gery, Brouilhet, and Olivier, 1968; Serre, Simon, and Claustre, 1970) to effectively reduce plasma and urine uric acid levels and to be a clinically effective drug in the treatment of gout. But, despite this fact, it has never been introduced into the United Kingdom. The mode of action of thiopurinol is not fully understood, but previous studies suggest that significant inhibition of xanthine oxidase does not occur *in vivo*, since the reduction on uric acid levels is not accompanied by increased excretion of xanthine and hypoxanthine as is the case with allopurinol. It has been shown that allopurinol therapy may be associated with:

- (1) Deposition of xanthine, hypoxanthine, and oxipurinol in muscle (Watts, Scott, Chalmers, Bitensky, and Chayen, 1971).
- (2) Xanthine nephropathy (Ablin, Stephens, Hirata, Wilson, and Williams, 1972).
- (3) Disturbance of pyrimidine metabolism with orotic aciduria and orotidinuria (Fox, Royse-Smith, and O'Sullivan, 1970), it follows that thiopurinol could have certain advantages over allopurinol, provided that clinical side effects and tissue incorporation could be ruled out.

In this study thiopurinol was administered to 2 patients with primary gout and to a third suffering from gout associated with a partial deficiency of HG-PRTase. In the former two patients an effective reduction of plasma and urine uric acid levels occurred *without* increasing xanthine and hypoxanthine excretion. In the latter case no effect on uric acid metabolism was observed—a result similar to that obtained by Kaplan (1970).

In duplicate studies in the pig, uric acid levels (normally low), were reduced during thiopurinol therapy, as were levels of allantoin, the principal urinary purine metabolite in this animal. In this laboratory studies with ¹⁴C thiopurinol and ¹⁴C allopurinol have shown no measurable tissue incorporation with either drug (Simmonds *et al.*, 1974); almost total recovery of radioactivity was obtained in urine and faeces alone. The finding that 36.5% of the radioactivity from orally administered thiopurinol was recovered in the faeces, compared with only 7% in the case of allopurinol, suggests that thiopurinol is less well absorbed from the gastrointestinal tract.

Thiopurinol appeared to have no immediate effect on pyrimidine metabolism as judged by levels of orotic acid excretion in man or in the pig. *In vitro* studies showed that no major metabolites of thiopurinol were found in intact human or pig erythrocytes.

Discussion

DR. S. KRANE (*Boston and Oxford*) There is some evidence that allopurinol, and undoubtedly thiopurinol, has an action of turning off *de novo* purine synthesis by binding PRPP. They have now shown that PRPP levels determine the activity of the aggregate of PRPP amino-transferase and that the lowering of PRPP levels by a drug such as allopurinol or thiopurinol would then decrease the activity of the dispersed enzymes. So it is not the nucleotide that regulates the biosynthesis but the level of PRPP, not only acting as substrate, but by determining the total activity of the enzymes. That would make more sense, since in the patient with PRPP deficiency it would also not reduce the level of PRPP at this site of synthesis.

DR. SIMMONDS We don't agree because we feel it is the availability of the PRPP in the body that is important. We have found enormous formation of allopurinol which must require a tremendous amount of phosphate of one form or another to form it and we have not been able to measure the PRPP levels as these are too low to detect any difference. In the cases of orotic aciduria where there must also be a tremendous availability of PRPP you do not find gout or overproduction of purine. There are anomalies which I think require investigation before you can stand up and say this is the effect.

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Withdrawal of Allopurinol in Patients with Gout. By W. Y. LOEBL and J. T. SCOTT (*Charing Cross Hospital and Kennedy Institute of Rheumatology, London*) Published in full in the *Annals* 1974, 33, 304.

Kinetics of Salicylate Metabolism. By T. GIBSON, G. ZAPHIROPOULOS, J. GROVE, B. WIDDOP, and D. BERRY (*Department of Rheumatology and Poisons Unit, Guy's Hospital, London*)

The major metabolites of aspirin, salicylic acid (SU), and salicyl phenolic glucuronide (SPG) are rate limited in their formation (Levy and Tsuchiya, 1972). With increasing doses of aspirin their synthesis and excretion approach a zero order process (i.e. unlike the metabolic products of most drugs which are formed by a first order process, their rate of biosynthesis does not increase in direct proportion to the dose of drug and will not increase further when a critical ceiling dose is exceeded. This is presumably due to enzyme-substrate saturation).

The reported variable plasma salicylate levels achieved in different subjects given the same dose of aspirin have a number of known causes (Cummings and Martin, 1964). Added to these may be an individual variation in the

capacity for producing and excreting the major metabolites, particularly salicylic acid (Paulus, Siegal, Mongan, Okun, and Calabro, 1971).

To examine this hypothesis 9 subjects with active rheumatoid arthritis or painful spinal disorders were given 65 mg/kg body weight aspirin daily in divided doses for 5 days. Plasma salicylate levels were estimated 2 hours after each midday dose. Urine was collected continuously for estimation of salicylic acid, salicyl phenolic glucuronide and salicylic acid.

In 4 subjects the study was extended to 11 days with the dose of aspirin increased to 100 mg/kg for the last 3 days.

Plasma salicylate levels rose to a peak on the third or fourth day then levelled. There were individual differences in the plasma salicylate levels on day 3 or 4 (mean 19.9 mg/100 ml, range 13.3 mg–28.5 mg/100 ml). The differences could not be related to individual variations in SU excretion with this dose regimen and there was no difference between the mean levels of those with rheumatoid arthritis and those with noninflammatory backache.

Increasing the dose of aspirin to 100 mg/kg in 4 patients induced an expected rise in plasma salicylate levels reaching a mean value of 34.5 mg/100 ml (range 29.5–45.5 mg/100 ml) on day 11. An increase was also seen in the urine SU of all subjects, but this was of a small order and was least in the subject who had the highest plasma salicylate level. 3 of the 4 patients also showed some increase of SPG excretion but no increase occurred in the patient with the highest plasma salicylate level.

The proportion of SU and SPG in the urine declined during the period of increased dosage and there was a marked increase in the proportion of salicylic acid (SA).

Conclusion

In 9 subjects given 65 mg/kg bodyweight aspirin it was not possible to show any association between plasma salicylate levels and individual variations in salicylic acid excretion.

When the dosage was increased to 100 mg/kg in 4 subjects a capacity for increasing SU excretion was shown, but this was least in a patient who had the highest plasma salicylate level. In the same patient the capacity for SPG formation was apparently exceeded by the higher dose and it is possible that the more limited capacity for SU and SPG formation in this case was responsible for the comparatively high plasma salicylate level.

At the higher dose of aspirin the proportion of SU and SPG in the urine declined in all 4 subjects reflecting the decreasing capacity for their formation. A compensatory increase in unchanged salicylic acid excretion was seen and this assumes a more important excretory role with increasing dose of aspirin.

Discussion

DR. W. C. DICK (*Glasgow*) Firstly, in view of the recent reports of possible hepatotoxicity of aspirin, did you take the opportunity of measuring liver enzymes after treatment as well as before? Secondly, did you relate your findings in any way to the albumin concentration; and finally, I would take issue with the word significant. I think the numbers are too small and the range too large for you to use the word significant in a statistical sense. There is certainly insufficient data to be certain of a lack of difference between rheumatoids and patients with backache.