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INTERMITTENT CONTROL OF HYPERURICAEMIA IN THE TREATMENT OF GOUT

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Spontaneous nucleation and growth of urate crystals require a high degree of supersaturation. Dissolution rates are rapid compared with those of growth, suggesting that periodic short-term reduction of urate might be effective treatment.

50 patients with gout were randomly allocated to one of two groups, receiving allopurinol either continuously or for 2 months every year. Patients with renal functional impairment or tophaceous gout were excluded. Duration of treatment ranged from 2-5 years. Of 24 patients in the continuous group 4 defaulted from follow-up. Of 26 patients in the intermittent group 6 defaulted, leaving 20 patients for study in each group.

Urate levels fell during treatment periods and rose after stopping the drug. Acute gouty arthritis occurred to a similar degree in the two groups during the first year, but thereafter attacks occurred with diminishing frequency in the continuous group compared with the intermittent group. 3 patients in the intermittent group were particularly troubled by severe gout occurring during periods of urate reduction. 4 patients in the intermittent group went on to continuous treatment at their own request because of recurrent attacks of gout. No significant change in renal function has occurred in either group during the period of study.

It is concluded that intermittent administration of allopurinol as given here is less effective in controlling symptoms of gout than continuous therapy.

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Effect of some purine metabolites contained in oyster on platelet aggreation

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Taurine, the main component of oyster, recovered the glucose tolerance in alloxan diabetic rats, and also have an important effect to V.B6 deficiency.
In recent experiment, the action of many purine derivertives in oyster to platelet aggregation were studied.
These substances, for example, adenosine, hypoxanthine and also 3-hydroxy anthranilic acid, the precursor of xanthurenic acid that is main product of tryptophan metabolism in V.B6 deficiency showed the same suppresive action to platelet aggregation.

Reference
On the effect of oyster components to platelet aggregation to some metabolites of amino acids
T.Ohta et al
The Fourth Symposium on Trace Nutrients Research, Kyoto 1987
Japan Trace Nutrients Research Society

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THE SOLUBILITY OF URIC ACID AND MONOSODIUM URATE IN URINE

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We measured the solubility of uric acid and monosodium urate in the concentrated urine obtained by the Fishberg concentration test and obtained fairly reproducible results. The solubility of uric acid in the concentrated urine samples showed an exponential increase with increasing pH. The solubility of monosodium urate showed a inverted V-shaped curve with a peak near pH 5.5. On the acidic side of this peak, the solubility decreased rapidly with decreasing pH, but on the alkaline side, it decreased gradually with increasing pH.

These results indicate the necessity of re-evaluating the concept of urine alkalization. The greater portion of uric acid exists in the form of urate in the urine, because its pKa, about 5.47, is in the lower half of the range of physiological changes in urine pH. Therefore, it is important to determine the solubility of urate, as well as that of uric acid. Since uric acid ions are affected by corresponding cations in the pH range on the alkaline side from the pKa, the solubility of total uric acid must be considered, with emphasis placed on urate, rather than uric acid.

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STOP-FLOW STUDIES ON TUBULAR TRANSPORT OF URIC ACID IN RATS

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The species differences in renal tubular transport of uric acid are well known. Among various nonhuman mammalian species, rats belong to a group with a reabsorptive net flux of uric acid in the renal tubules, and hence they have sometimes been used to test uricosuric activity by a clearance technique. The stop-flow technique is also regarded as a useful method for evaluating drug effects on tubular transport of uric acid. This technique has been used with rabbits, dogs and cebus monkeys, but not with rats. Reported here is the utility of a stop-flow technique using rats. The fractional excretion value of uric acid (FEua) in rats with a high urine flow rate was nearly 1.0, which was clearly higher than those in clearance experiments. On the other hand, in pyrazinoic acid (PZO)-treated rats with inhibited secretion of uric acid, the FEua value was much lower than that in non-treated rats, and the stop-flow patterns always indicated a remarkable reabsorption of urate in the proximal tubules corresponding to the secretion of p-aminohippurate. As generally accepted, uricosuric drugs inhibit bidirectional transport of uric acid in the renal tubules. We describe the characteristics of uricosuric drugs using stop-flow techniques with PZO-treated and non-treated rats, and the uricosuric properties of a new uricosuric diuretic, S-8666, which has been developed in our laboratories.

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Improved assay method of dTMP synthase in rat liver and its application to human lung cancer cells.

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A simple micromethod was established for the accurate measurement of dTMP synthase activity in rat liver crude extracts. The reaction product of dTMP synthase assay,i.e.,tritiated water,released from (5-3H)deoxyuridine 5'-monophosphate(dUMP),was separated in one-step with 100% KOH absorption from (5-^{3}H)deoxyuridine (dUrd) which is the side-product of dephosphorylation of (5-^{3}H)dUMP during the enzyme reaction. Tritiated water was trapped in three droplets of 100% KOH deposited on the underside of the vessels' lids,while (^{3}H)dUrd remained in the bottom of vessels after absorption of (5-^{3}H)dUMP from the reaction mixture by charcoal treatment. Under standard assay conditions in the crude extracts of rat liver,the specific activity of dTMP synthase and dUMP phosphatase were 0.092±0.002 and 0.351±0.013 nmol/hr/mg protein,respectively. This method was also adapted for dTMP synthase assay in human lung cancer cells.The major advantages of this method are the elimination of the phosphatase activity which interferes with the estimation of dTMP synthase activity,one-step separation of ^3H_2O,high sensitivity, high reproducibility and low requirement of tissue.

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FURTHER EVIDENCE FOR A 'NEW' PURINE DEFECT,INOSINE TRIPHOSPHATE (ITP) PYROPHOSPHOHYDROLASE DEFICIENCY.

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Raised levels of an unusual nucleotide were found in the erythrocytes of 3 members of a consanguinous kindred in which the propositus presented with immunodeficiency due to ADA deficiency. 3 siblings, the parents and 7 of 9 relatives were heterozygotes. This nucleotide and a corresponding diphosphate, were identified as ITP (mean 157μmol/l) and IDP (mean 28μmol/l) by their HPLC characteristics pre/post degradation. They have not been seen in 1000 other subjects. ITP formation from radiolabelled precursors was also investigated. The 3 subjects with raised ITP levels accumulated up to 50% of the counts in ITP/IDP, 7 of 8 other family members had a mean of 21%. Only 6% of control erythrocytes showed any such incorporation (11-25%).

These results accord with those of Vanderheiden (Nature 1967;216:1036-7) who found high erythrocyte ITP levels in 7 of 6000 persons studied, 2 of whom were siblings. Henderson et al (Can J Biochem 1977;55:359-64) also showed that erythrocytes of 5% of controls accumulated relatively high amounts of ITP from radiolabelled precursors. This was ascribed to a deficiency of a specific ITP pyrophosphohydrolase (EC 3.6.1.19:ITPase) which followed a co-dominant pattern and suggested a cycle in which ITP was continuously synthesised and degraded. The finding of this defect in a large kindred provides a unique opportunity to investigate the inheritance of ITPase deficiency and the activity of the putative 'inosinate cycle', as well as the clinical significance of ITP accumulation, in more detail.