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The Metabolic Basis of Uric Acid Stone Formation

By O. M. WRONG. (*Department of Medicine, University of Dundee, Dundee, U.K.*)

The two main factors known to be associated with uric acid calculi are: (1) a high urinary concentration of uric acid/biurate, caused either by an increased urinary excretion or a decreased urinary volume; (2) a urine persistently in the more acid range under pH 6.0 (urine pH normally shows fluctuation between 4.6 and 8.0). The pK_1 of uric acid is in the region of 5.6. Uric acid and biurate both tend to form supersaturated solutions in urine, but the solubility of biurate is about 17 times that of uric acid, and precipitation is therefore more likely to occur from urines which are more acid, especially under pH 5.6.

In Western Europe, U.S.A. and Israel the majority of adult patients with uric acid calculi show no increase in uric acid/biurate, but a highly significant decrease in urine pH. The cause of this more-acid urine is still uncertain, but there are several explanations (which will be reviewed) and the mechanism may not be the same in all patients.

Alkalinization of the urine, with oral sodium

bicarbonate or citrate, is the most important principle in the prevention of further attacks of uric acid calculi, and is very effective.

Amino Acid Metabolism in Cystinuria

By M. D. MILNE. (*Department of Medicine, Westminster Medical School, 17 Page Street, London S.W.1, U.K.*)

Cystine calculi account for about 1% of urinary stones in adult life, but a relatively higher proportion in childhood. Cystinuria is an autosomal recessive hereditary disease, the frequency of homozygotes in the general population being approx. 1 in 20000. The maximum solubility of cystine in urine of pH 4.5–7.0 is about 300 mg/l. As adult cystinuric patients usually excrete 600–1300 mg of cystine daily, the amino acid often crystallizes and may form calculi. The peak age of clinical presentation is in the third decade, but about 8% of patients have symptoms and signs of calculi before the age of 10, and in a few patients calculi are first formed in extreme old age. The disease considerably decreases life expectancy, the mean age of death in a recent series being 52 in males and 64 in females. In addition, cystinuria causes considerable discomfort and disability from renal colic, chronic pyelonephritis and, eventually, chronic renal failure. Cystinuric patients often have to submit to repeated surgical operations for removal of calculi. Factors increasing the liability to stone formation are oliguria, a highly acidic urine, a high protein diet, and urinary obstruction and infection. Many of these factors are controllable, and therapy with a high-fluid regime undoubtedly lessens the tendency to form renal stones. Calculi, however, are especially liable to form during sleep, when the urine is of maximum acidity and osmolality. Effective fluid therapy must, therefore, inevitably interfere with sleep, as it is of particular importance to preserve a dilute and copious urine flow throughout the whole 24 hours. In unco-operative patients in whom there is stone formation despite attempts at a high-fluid regime, penicillamine therapy is necessary to decrease urinary cystine output. The main urinary sulphur-containing amino acid during effective penicillamine treatment is the mixed disulphide of penicillamine and cysteine. Because of the asymmetry of the molecule, this compound is much more soluble than is cystine.

It is now generally agreed that the basic abnormality of the disease is an impaired transport capacity for cystine, lysine, arginine and ornithine by the proximal renal tubular cells and by the intestinal mucosa. Were it not for the relative insolubility of cystine in urine, cystinuria would be a completely harmless metabolic anomaly. The

renal transport defect is easily proved by determination of the clearance of the four affected amino acids. These are all grossly increased up to values sometimes equal to the glomerular filtration rate despite plasma concentrations of the amino acids which are either normal or low. Proof of defective intestinal absorption has been given by: (a) failure of concentration of the amino acids when intestinal mucosa from cystinurics is incubated *in vitro*; (b) lower plasma concentrations of the affected amino acids after their oral ingestion, combined with a normal plasma decay curve after intravenous injection; (c) detection of unabsorbed amino acids in faeces, or of products of their bacterial degradation both in faeces and in urine; (d) intubation experiments with direct demonstration of an abnormally slow disappearance of the affected amino acids from the gut lumen. Bacterial degradation products from lysine include pentamethylenediamine (cadaverine) and piperidine, and from arginine, citrulline, ornithine, tetramethylenediamine (putrescine) and pyrrolidine. All these compounds have been detected in excess in the urine, the faeces, or in both, of cystinuric patients. Dietary cystine is mainly degraded to inorganic sulphate. Urinary sulphate increases later after oral administration of cystine in cystinuric patients as compared with controls, owing to the delay in the unabsorbed amino acid reaching the colon.

Cystinuria has been shown to be due to at least three abnormal allelic genes at the same chromosomal locus. The easiest method of differentiation between different types of cystinuria is by examination of the urine of heterozygotes in the affected families. In the completely recessive form of the disease, the urine of heterozygotes is normal, whereas in the incompletely recessive type, hetero-

zygotes excrete excess of cystine and lysine, but not of arginine or ornithine. The cystine output is too low for crystallization and stone formation to occur. In the former, more common type the intestinal transport defect of homozygotes is especially severe. Despite the fact that lysine is an essential amino acid, cystinuric patients show no obvious nutritional impairment. This apparent paradox has now been explained by the dual mechanisms of absorption by the gut of the products of protein digestion. Free amino acids are absorbed by an active transport process, with concentration of the amino acid within the mucosal cell above that either in the lumen or in the portal capillary blood. In addition, oligopeptides may be taken up by the cell by a process independent of that involving the free amino acids. The peptides are then hydrolysed either in the brush border or in the cell interior, and delivered to the portal capillary blood as the constituent free amino acids. Only the free-amino-acid transport mechanism is impaired in cystinuria, allowing normal nutrition to be maintained by a normal capacity for oligopeptide uptake. Thus, after ingestion of the dipeptide lysylglycine, plasma lysine in cystinurics increases more rapidly than after oral intake of a corresponding equimolecular mixture of free lysine and glycine. Similarly, plasma concentrations of both arginine and of lysine increase more rapidly after oral casein than after a mixture of free amino acids derived from the protein by complete hydrolysis.

In summary, although cystinuria is a somewhat rare disease causing only a small proportion of urinary calculi, it is of disproportionate interest and importance in the study of the mechanisms of amino acid transport, a process that is still poorly understood.

COMMUNICATIONS

Influence of Plasma Lipids on the Activity of Lipoprotein Lipase

By PHILIP E. BRUMBY. (*National Institute for Research in Dairying, Shinfield, Reading, Berks., U.K.*)

Bovine milk lipoprotein lipase hydrolyses the triglycerides of human plasma lipoproteins but not those of bovine or guinea-pig plasma lipoproteins. Resistance to hydrolysis may not be entirely due to the protein component, though this is known to be important in relation to the activity of lipoprotein lipases (Fielding, 1970b; Fielding, Lim & Scanu, 1970; LaRosa, Levy, Herbert, Lux & Fredrickson, 1970) as an activated emulsion of the lipid from bovine plasma lipoprotein is also a poor substrate. Further, incorporation of bovine plasma lipid at a

concentration of 30% into a soybean-oil emulsion (89% triglyceride, 11% egg lecithin), an effective substrate, decreases the rate of hydrolysis to about 50% that of the control.

Tests on the rates of hydrolysis after incorporation of the major components of plasma lipid into the soybean-oil emulsion have shown that cholesterol esters, phospholipids and free cholesterol all cause decreases. Phospholipids, and particularly cholesterol, were the most effective. Phospholipids in the substrate at concentrations of 20, 30 and 50% decreased the relative activity by 10, 60 and 80% respectively, whereas cholesterol at 2.5, 5, 10 and 30% caused decreases of 30, 40, 80 and 95% respectively.

In similar studies, increasing the amount of incorporation of phospholipids at fixed concentra-