

The excretion of indolic acids and its relation to Hartnup disease

MD Milne [1959]

Summary of papers read at the meeting on June 17th 1959

The excretion and clearance of many well-known drugs is a function of urinary pH, weak acids being excreted more rapidly in alkaline urine, and weak bases in acid urine. These drugs include the bases, mepacrine, chloroquine, quinine, procaine, mecamlamine and pempidine, and the weak acids salicylic acid and phenobarbitone. Ammonia is the only naturally-occurring substance in human urine to behave in this fashion, but this is not a true example of excretion since urinary ammonia is synthesised in the distal tubular cells and is not derived from arterial blood. Evidence was presented showing both endogenous and exogenous indolyl-3-acetic acid, but not 5-hydroxyindolyl 1-3-acetic acid is excreted more rapidly in alkaline urine. This influences the relative amounts of indolylacetic acid and of its conjugate, indolyl-3-acetylglutamine in urine. The former predominates in alkaline urine, the latter in acid urine.

Hartnup disease is a recessive hereditary metabolic disorder characterised by pellagra, attacks of cerebellar ataxia, a generalised renal aminoaciduria, and excess excretion of indican, indolylacetic acid and indolylacetylglutamine. Metabolic studies were carried out on two cases of the disease in a state of mild metabolic alkalosis with alkaline urine of constant pH, thus removing any possibility of variation of excretion of indolylacetic acid from changes in urinary pH. After ingestion of large doses of L-tryptophan, cases of Hartnup disease excrete less kynurenine and more indolic acids than normal subjects. Excretion of large amounts of indolylacetic acid continues for more than 24 hours, whereas the output in normal controls falls to basal levels within 8 hours. Urinary indican behaves similarly, being excreted in excess for long periods

in Hartnup disease. Corresponding abnormalities were found in the metabolism of DL-tryptophan. The results strongly suggest that there is a primary abnormality of tryptophan transport in Hartnup disease, and probably of other aminoacids in addition. The defect certainly involves the cells of the proximal renal tubules and of the jejunal mucosa, and possibly also the liver parenchymal cells. It was suggested that further research in Hartnup disease might increase our present very limited knowledge of the mechanisms of amino acid transport. The cerebellar ataxia of Hartnup disease may possibly be due to intoxication by retained indolic acids. If this is proved correct, alkalinisation of the urine by sodium bicarbonate would increase their excretion and provide a simple and innocuous means of therapy. The pellagra is explained by reduced oxidation of tryptophan to kynurenine, since this is an intermediate in the conversion of tryptophan to nicotinamide.

Commentary

My choice of a paper by Malcolm Milne is I admit personal.

Milne [President of the Renal Association, 1965-68] was a senior lecturer at Hammersmith Hospital in the late 1950s when he looked after my own father [who had membranous nephropathy], and then was professor of medicine at Westminster when I was a clinical student in the early 1970s.

He was a man of few words and dry wit, crisply delivered in a Mancunian accent. To medical students his intimidating intellect was not immediately apparent - until we saw him in action at hospital rounds, when he showed little mercy when junior [or senior] staff were poorly briefed or imprecise. He was happiest on ward rounds discussing with us the finer points of tubular handling of potassium and amino acids, and was I think rather mystified by the 'new nephrology' - there was a haemodialysis programme emerging on his unit under the leadership of his senior lecturers and senior registrars; he was far from convinced dialysis would ever have a worthwhile therapeutic application.

This understated paper from 1959 is characteristic of its era, reporting careful metabolic analysis in a very rare disease in only a few patients [n = 2 !].

Hartnup disease was first described in London in 1956 [1] , and Milne's observations in this paper are the basis of his seminal QJM paper of 1960 [2] in which he

established the pathophysiology of Hartnup disease, and also opened a broader understanding of amino acid handling.

As it happens Milne's speculation that sodium bicarbonate therapy would be useful has not been borne out, and supplementation with nicotinamide and tryptophan [via a high protein diet] suffice.

It took another 45 years before the mutation underlying Hartnup disease, in the neutral amino acid transporter, B⁰AT1, was identified in a Nature Genetics paper with 27 authors [3], quite a contrast to the solo or small authorship more typical of the 1950s.

- 1. Baron DN, Dent CE, Harris H, et al; Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal amino-aciduria, and other bizarre biochemical features; Lancet. 1956 Sep 1;271(6940):421-8.**
- 2. Milne MD, Crawford MA, Girao CB, Loughridge LW. The metabolic disorder in Hartnup disease. Quart J Med 1960;29:407-21.**
- 3. Kleta R, Romeo E, Ristic Z, Ohura T, Stuart C, Arcos-Burgos M, et al. "Mutations in SLC6A19, encoding B⁰AT1, cause Hartnup disorder". Nature Genetics 2004; 36: 999-1002.**