CC/NUMBER 30
JULY 23, 1984

This Week's Citation Classic™

Carson N A J & Neill D W. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland.
Arch. Dis. Child. 37:505-13, 1962.
[Royal Belfast Hosp. for Sick Children, and Royal Victoria Hosp., Belfast, Northern Ireland]

During screening of mentally retarded persons in Northern Ireland for metabolic disorders using simple qualitative tests and two-way paper chromatography, two sisters were discovered to be excreting homocystine, a previously unrecognised metabolic error. [The *Science Citation Index* (*SCI*®) and the *Social Sciences Citation Index*® (*SSCI*®) indicate that this paper has been cited in over 195 publications since 1962.]

Nina A.J. Carson
Department of Biochemistry
Royal Victoria Hospital
Belfast BT12 6BA
Northern Ireland

June 28, 1984

"In the 1950s, while working in a children's hospital laboratory, I became interested in developing paper chromatographic techniques to screen patients with suspected amino acid disorders. In 1959, I was given a research grant to extend this work and screen the mentally retarded population of Northern Ireland for metabolic errors. During this research, two sisters were discovered who appeared to be excreting cystine in their urine. I had the opportunity to examine the children and was impressed by the similarity and unusual nature of their symptoms, i.e., mental retardation, fits, ectopia lentis, and skeletal abnormalities (they both later died as a result of thrombotic episodes).

"Chromatographic examination of urine specimens which had shown a normal amino acid pattern when fresh, after two weeks' storage, revealed large spots in the cysteic acid position. The urine was also found to give a positive nitroprusside/cyanide test, suggesting the presence of a sulphur-containing amino acid. It is known that the phenol solvent which we used is detrimental to thiol groups but not to the oxidised product. This would explain the presence of the normal amino acid pattern on the fresh specimen of urine. As it is unusual to find a specific cystinuria without the presence of the basic amino acids lysine, orithine, and arginine (all three were absent in these children), and as I did not possess an amino acid analyser, the specimens were sent to Dent at University College, London. In the meantime, the children were given a cystine load. On examination of the postload urines using large size chromatography paper and oxidising with hydrogen peroxide, two spots were evident, one of which co-chromatographed with cysteic acid. Dent, while first confirming our finding of cysteic acid, telegraphed excitedly a few days later that what we had was homocysteic and not cysteic acid.

"This experience highlights the fact that no one person is responsible for any new discovery. The children were referred to me by Claude Field, paediatrician, because he suspected the presence of an inherited metabolic disorder. My colleague and mentor D.W. Neill, senior biochemist, encouraged me to pursue the investigation, and Dent and his co-workers with their expertise in amino acids were responsible for the undoubted identification of homocystine. Other patients were discovered in Northern Ireland and a typical clinical picture emerged.

"In 1964, Mudd *et al.*[1] reported that homocystinuria was due to inactivity of cystathionine synthase (CS), an enzyme on the trans-sulphuration pathway which converts homocystine to cystathionine. Since then, three genetically determined enzyme defects are now known in the remethylation pathway from homocystine to methamine. (For a review of homocystinurias, see reference 2.)

"Treatment initially was by giving a low methionine diet, then Barber and Spaeth[3] in 1967 reported three patients on a normal diet who responded biochemically to pharmacological doses of B_6, thus establishing the original form of homocystinuria as an early example of a vitamin dependent inborn error. About 40 percent of our patients are B_6 responsive. The reason for this often quoted reference is therefore because we were the first group to discover CS homocystinuria. Later in 1962, Gerritsen, Vaughn, and Waisman[4] described the first North American patient."

1. **Mudd S H, Finkelstein J D, Irreverre F & Laster L.** Homocystinuria: an enzymatic defect. *Science* 143:1443-5, 1964. (Cited 215 times.)
2. **Carson N A J.** Homocystinuria—clinical and biochemical heterogeneity. (Cockburn F & Gitzelmann R, eds.) *Inborn errors of metabolism in humans.* New York: Liss, 1982. p. 53-67.
3. **Barber G W & Spaeth G L.** Pyridoxine therapy in homocystinuria. *Lancet* 1:337, 1967. (Cited 85 times.)
4. **Gerritsen T, Vaughn J G & Waisman H A.** The identification of homocystine in the urine. *Biochem. Biophys. Res. Commun.* 9:493-6, 1962. (Cited 125 times.)

