Comment

These investigations show that the oral administration of D(−)penicillamine can reduce or abolish the excretion of cystine in cystinuric patients. The cysteine residues are excreted, as is the D(−)penicillamine cysteine mixed disulphide, which is more soluble in water.

These observations suggest that the use of D(−)penicillamine may have therapeutic value in the management of patients with cystinuria who are prone to the development of urolithiasis. We are investigating further the long-term effects of the use of D(−)penicillamine in cystinuria, and further studies on this, and on the mechanisms of action, will be reported later in greater detail.

Summary

Disulphide exchange reactions with thiols and other disulphides suggested that the excessive excretion of the insoluble disulphide amino-acid cystine might be modified by the administration of a suitable thiol.

Penicillamine has been administered to two patients with cystinuria.

The daily urinary cystine excretion was measured both gravimetrically and by isotope dilution.

The cystine excretion was shown to be abolished or reduced according to the dose of penicillamine administered.

During penicillamine administration two new substances appeared in the urine which on chromatographic evidence are penicillamine-cysteine disulphide and penicillamine disulphide.

The greater solubility of these compounds in water offers a new therapeutic approach to the prophylaxis of urolithiasis in cystinuria.

We are pleased to acknowledge the collaboration of Dr. H. E. Archer in the exploratory experiments, and the technical assistance of Miss E. D. Bell, Miss D. R. Gibbs, and Mr. L. Rawlings. We are indebted to Dr. C. A. Lewis for information on the chromatographic solvent systems employed.

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The Scottish Home and Health Department, in consultation with the medical profession in Scotland and the Scottish Association of Executive Councils, is to introduce experimentally in the counties of Renfrew, Perth, and Kinross a revised type of medical card. It is designed with a pouch to carry a personal medical record card. It has space for entries by the patient's family doctor, hospital or clinic doctors, and (in the case of schoolchildren) school doctors. In it can go data which should be available to any doctor into whose care a patient might come, for example, in emergency. The revised type of card will be issued only as and when a new medical card would have been required in normal course—that is, for infants, new patients coming into the area, on change of doctor, etc. Under the present arrangements patients are required to show their medical card to their doctor if he asks to see it, and there is evidence of many cases where medical cards are mislaid or lost. It is hoped the experiment will help the efficient care of patients and also encourage safer custody by patients of their medical card.

STATURE AND NUTRITION IN CYSTINURIA AND HARTNUP DISEASE

BY

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Andrews (1952), in a review of cystinuria, stated: "Cystinurics are in general persons of somewhat less than average stature. While not to be described as dwarfs in any sense of the word, cystinurics have always been of somewhat slight build." He did not, however, publish any figures confirming this impression. In a recent metabolic study of cystinuria (Asatoor *et al.*, 1962), one of us (J. E. C.) independently noticed that many of the patients were below the average height for age and sex. As cystinuria is an important disease of amino-acid metabolism, with possible effects on general nutrition, it was thought worth while to make a more detailed survey of the heights of cystinuric patients. Similar studies were made in the closely allied but much more rare condition, Hartnup disease (Baron *et al.*, 1956).

Methods

Heights were measured in 44 cystinuric patients. All of them, except two children, gave a history of urinary calculus disease and were thus presumably homozygotes (Dent and Harris, 1951; Harris and Warren, 1953; Harris *et al.*, 1955). The two exceptions were shown by paper chromatography to be excreting large quantities of cystine, lysine, arginine, and ornithine, and were therefore homozygotes who had not yet developed clinical symptoms of the disease. Twenty-one of the patients were personally observed by us, and the heights of the other 23 were kindly supplied by physicians and surgeons known to be in clinical charge of cystinuric patients.

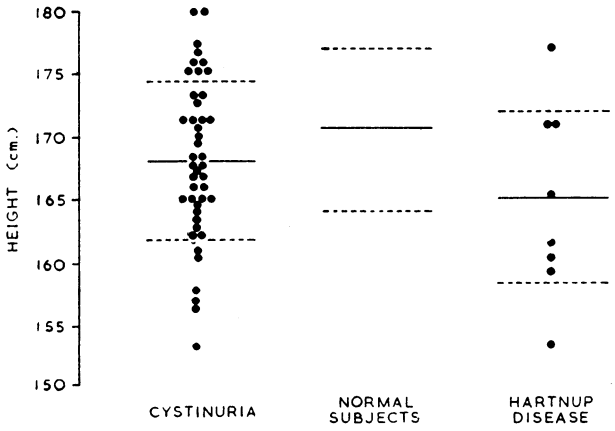
Only 15 cases of Hartnup disease have been described to date, and only eight of these could be traced by postal inquiry. Heights of these patients were obtained either from the patients themselves or from their parents. The data in Hartnup disease are neither as complete nor as accurate as those in cystinuria, but are thought worth reporting.

Control heights of the normal population were obtained from the paper by Clements and Pickett (1957), which reports data from 25,000 males, and from a publication, *Women's Measurements and Sizes* (1957). reporting data obtained from 5,000 women. Normal heights of children were obtained from Stuart and Stevenson (1959). The observed heights were expressed as deviations from the expected mean for age and sex, but have been graphed (see Chart) as corrected heights for normal adult males with a mean height of 170.3 cm. ±6.5 cm. (Clements and Pickett, 1957).

Results

The data are shown in the Chart. The mean height of the cystinuric patients is 2.5 cm. less than the mean of normal subjects, and that of the patients with Hartnup disease 5.3 cm. less. The standard deviations in both

cases are almost identical with the standard deviation of the normal population. The differences are statistically significant in both cases at the 0.05 probability level (Table I).



Heights of cystinuric patients and of patients with Hartnup disease compared with normal subjects. Heights of children and of adult females have been corrected to figures for adult male subjects. The continuous lines give the means and the broken lines the standard deviations. The height of cystinuric patients is on an average 2.5 cm. less than that of normal subjects and that of patients with Hartnup disease 5.3 cm. less.

TABLE I.—*Statistical Analysis of Heights of Cases of Cystinuria and Hartnup Disease Compared with Normal Heights*

Disease	Mean Height (cm.), Adjusted to Adult Male Population	Mean Height Normal Adult Males (cm.)	t	P
Cystinuria ..	167·8	170·3	2·10	<0·05
Hartnup disease	165·0	170·3	2·13	<0·05

Discussion

Cystinuria and Hartnup disease are closely allied hereditary disorders of amino-acid transport. In both cases a transport defect has been shown to occur in the proximal renal tubules (Dent and Rose, 1951; Baron *et al.*, 1956) and in the jejunal epithelial cells (Milne *et al.*, 1960, 1961; Asatoor *et al.*, 1962). Different groups of amino-acids are involved in each disease—the dibasic amino-acids in cystinuria and many of the monamino-monocarboxylic amino-acids in Hartnup disease. The abnormal amino-acid excretion in cystinuria is obviously of direct clinical importance. Cystine is the most insoluble of the amino-acids derived from protein hydrolysis, and its precipitation within the urinary tract leads to calculus formation, often associated with pyelonephritis and progressive renal damage. With this exception, the amino-aciduria, although of great diagnostic value, has been regarded as a harmless metabolic anomaly.

This paper shows that patients with cystinuria and Hartnup disease are significantly below the normal height for age and sex. There are three possible reasons: (*a*) the abnormal genes responsible for the anomalies might be linked with genes controlling body height; (*b*) the clinical manifestations of the diseases during childhood might prejudice normal growth; or (*c*) the abnormality of amino-acid transport might be of direct nutritional significance. The first alternative is thought to be unlikely, but obviously cannot be excluded with absolute certainty. Only 20% of cystinurics suffer from clinical manifestations of the disease before growth is complete (Renander, 1941). The symptoms produced by Hartnup disease are of little inconvenience to the patient. The pellagra of the disease is controlled by nicotinamide therapy, and is in itself evidence of a nutritional defect. The attacks of cerebellar ataxia are relatively infrequent, and are too short-lived to prejudice growth and development.

Probably, therefore, the third alternative is the most likely. Table II gives available data of amino-acid loss in the urine in the two diseases. The amino-aciduria might be significant in that amino-nitrogen is lost from the body, or that there is a specific drain of essential amino-acids which cannot be synthesized from any other source. Lysine is the only essential amino-acid involved in the transport defect of cystinuria, whereas tryptophan, phenylalanine, threonine, valine, leucine, isoleucine, and methionine are involved in the defect in Hartnup disease. Table III gives the minimal and daily recommended intakes, and the known urinary loss of essential amino-acids and total amino-nitrogen in normals, cystinurics, and cases of Hartnup disease.

In addition to the known urinary loss of amino-acids in the two diseases there is a corresponding loss of unknown degree due to the intestinal absorption defect. The intestinal defect in cystinuria has been shown to involve cystine, lysine, arginine, and ornithine (Milne *et al.*, 1961; Asatoor *et al.*, 1962, whereas in Hartnup disease there is certain proof only of an absorption

TABLE II.—*Urinary Loss of Essential and Other Amino-acids in Cases of Cystinuria and Hartnup Disease (Grammes Per Day). Data Corrected to Figures Excreted by an Average 70-kg. Adult Male Patient*

Cystinuria

	Stein (1951)	Arrow and Westall (1958)	Doolan *et al.* (1957)	Mean and S.D
No. of cases	5	4	4	13
Lysine	2·3 1·0 1·98 2·38 1·35	0·94 0·60 2·58 1·57	1·94±0·72	1·73±0·68
Cystine	0·97 0·42 0·82 0·74 0·70	0·64 0·68 1·15 1·78	1·21±0·41	0·98±0·38
Arginine	1·24 0·55 0·92 0·77 0·67	0·65 0·50 1·55 1·05	1·15±0·26	0·96±0·31
Ornithine	0·42 0·18 0·36 0·50 0·42	0·19 0·25 0·62 0·57	Not estimated	0·39±0·16

Hartnup Disease

	Evered (1956)	Cusworth and Dent (1960)	Mean
No. of cases ..	2	1	3
Threonine ..	0·96 1·17	0·68	0·94
Valine	0·20 0·85	0·50	0·52
Methionine ..	0·07 0·16	0·06	0·10
Iso-leucine ..	0·24 0·52	0·30	0·35
Leucine ..	0·19 0·61	0·35	0·38
Phenylalanine ..	0·22 0·62	0·29	0·38
Lysine	0·10 0·19	0·29	0·19
Total amino-acid	10·4 12·4	9·00	10·6

TABLE III.—*Urinary Loss of Essential Amino-acids in Cystinuria and Hartnup Disease Compared with Requirements and Intake*

Disease	Amino-acid	Mean Urinary Loss (g.)	Minimal Daily Requirement (g.)	Recommended Minimal Daily Requirement (g.)	Amount Ingested in Ideal Diet (g.)
Cystinuria ..	Lysine	1·73	0·80	1·60	7·8
Hartnup disease	Threonine	0·94	0·50	1·00	4·6
,, ,, ..	Valine	0·52	0·80	1·60	6·9
,, ,, ..	Methionine	0·10	1·10	2·20	2·6
,, ,, ..	Iso-leucine	0·35	0·70	1·40	6·4
,, ,, ..	Leucine	0·38	1·10	2·20	10·8
,, ,, ..	Phenylalanine	0·38	1·10	2·20	5·2
Cystinuria ..	Total	5·00	35	70	100
Hartnup disease	Total	10·6	35	70	100

defect for tryptophan (Milne *et al.*, 1960; Shaw *et al.*, 1960). The other amino-acids excreted in excess in the urine in Hartnup disease are, however, also likely to be absorbed from the gut less efficiently than in normal subjects. Faeces from cases of Hartnup disease often contain excess leucine, isoleucine, valine, and phenylalanine in addition to tryptophan (Milne, unpublished observations, 1962), a finding highly suggestive, although not conclusive, of reduced jejunal absorption. The unabsorbed amino-acids are either passed unchanged in the faeces or are metabolized by bacteria to products —for example, diamines, indole, and indolic and phenolic acids—which are of no value nutritionally, and are excreted either unchanged or as metabolites in the urine. Probably, therefore, there is some deficiency of available essential amino-acids in both cystinuria and Hartnup disease which results in the reduced growth of the patients (see Chart). All these patients were living either in Western Europe or the U.S.A. with satisfactory protein diets. Presumably the metabolic defects of cystinuria and Hartnup disease would be of greater nutritional significance if occurring in less privileged communities or in times of rationing or famine.

Although most cases of cystinuria have no clinical symptoms except those due to renal calculus disease, there are several case records of unexplained associated conditions. Gross *et al.* (1958) review their work on lysinuria in hereditary relapsing pancreatitis. The urinary amino-acid pattern was not then claimed to be that of cystinuria. They have now published (Gross *et al.*, 1962) details of a family with hereditary pancreatitis who also had the typical urinary abnormalities of cystinuria, with excretion of cystine up to 848 mg./day and of lysine up to 1,669 mg./day. Visakorpi and Hyrske (1960) record the association of cystinuria, severe mental deficiency, and epilepsy. Berry (1959) has published details of a family in which three siblings had cystinuria, mental deficiency, and atypical osteogenesis imperfecta. There was a correlation between the severity of the urinary amino-acid loss and the associated abnormalities.

Protein restriction is obviously contraindicated in the treatment of both conditions. A low methionine diet (Smith *et al.*, 1959) has been advised in the management of cases of cystinuria, as this is the most certain method of reducing cystine output. It would, however, be difficult to curtail methionine intake without also reducing that of lysine. In especially severe cases where some protein restriction seems to be essential to reduce cystine excretion (Smith *et al.*, 1959), lysine supplements would be a logical therapeutic addition. The high fluid regime of Dent and Senior (1955), with or without alkalinization of the urine to increase the solubility of cystine, is theoretically a better method of treatment. Similarly, protein should not be restricted in the management of Hartnup disease, except possibly for short periods to control the cerebellar symptoms of the disease. These are probably due to temporary intoxication from products of bacterial degradation of unabsorbed amino-acids within the colon, and should respond to partial sterilization of the gut with neomycin or other antibiotic. The diet in both conditions should ideally contain considerable amounts of first-class protein, with some restriction of protein of less biological value. If there is evidence of severe dwarfism in a child with cystinuria, a trial of small amounts of lysine hydrochloride at a dosage of 1 to 2 g. three times daily would be a logical nutritional supplement. This therapy would, however, have the disadvantage of acidifying the urine, and should be accompanied by oral sodium bicarbonate.

Summary

The heights of patients with cystinuria and Hartnup disease are on an average below that of the general population. It is suggested that this is due to a mild nutritional disadvantage during childhood resulting from loss of essential amino-acids in the urine and less efficient absorption of the amino-acids from the gut. The relevance of these facts in relation to the clinical management of the two diseases is discussed.

Thanks are expressed to Dr. G. W. Frimpter, Dr. L. Hradcová, Dr. M. G. McGeown, and Professor L. N. Pyrah for data of heights of cystinuric patients, and to Professor H. Bickel, Dr. N. R. Butler, Professor C. E. Dent, and Dr. A. D. Leigh for permission to contact the patients with Hartnup disease.

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