CYSTINURIA

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Cystinuria is a congenital abnormality resulting from failure to carry out protein metabolism in a normal way. Cystine is a sulphur containing amino acid which is present in many different foods. In normal metabolism it is broken down to simpler constituents and excreted in the urine as sulphates. Cystinurics are unable to complete this oxidation process and so excrete cystine unchanged.

The urine of normal people contains only a faint trace of cystine, insufficient to be detected by the usual clinical tests. Cystinurics may excrete up to 1 gm. of cystine per day, the amount varying with the diet. Cystine is a relatively insoluble amino acid and easily forms crystals in the urine. If these are retained in the kidney or bladder they may form calculi, but not all cystinurics precipitate crystals and not all who form crystals develop calculi.

Cystinuria is a hereditary defect, being transmitted by either parent to children of either sex. It behaves as a recessive Mendelian factor. In some cases of cystinuria it is easy to show that other members of the family are likewise affected but evidence of this may be absent or at any rate very difficult to obtain.

Little is known of the incidence and distribution of cystinuria, since unless calculous disease supervenes the abnormality causes no symptoms and is only likely to be discovered by a chance urine test. It is certainly a rare abnormality, though not so rare as has been supposed. Lewis (1932) made a special search for cystinurics by examining the urine of over 10,000 young men and women, mostly college students, and found crystals of cystine in four individuals only. These were the only cases which would have been discovered by microscopic examination alone, but by using chemical tests also he found 14 others who were excreting an excess of cystine, though their urine did not contain crystals. These 18 individuals were all in good health, with no signs or symptoms to suggest calculous disease. Probably none of these cystinurics would have been discovered but for the accident of their inclusion in this research.

Pathology

The amount of cystine in the urine of a cystinuric can be augmented by increasing the

protein in the diet, and it might be expected that if pure cystine were administered to a cystinuric the excretion of cystine would be still further proportionately increased. But this does not always occur. Some cystinurics seem to be able to oxidize pure cystine administered with food and yet are not able to cope with cystine-containing foods. In fact, if cystine is extracted from the urine of a cystinuric and then administered to the same individual he may now be able to oxidize it completely to sulphates.

This apparent paradox is explained by experiments which go to prove that the cystine in the urine of a cystinuric is not derived directly from protein cystine, but from another sulphur containing amino acid, methionine. Evidence in support of this is provided by the fact that when methionine is administered to a cystinuric the urinary cystine is increased proportionately. Methionine may not be the only source of urinary cystine but Brand, Block and Cahill (1937) have shown that the cystine of urine is derived in part at least from that portion of protein sulphur which is present in the form of methionine.

The excretion of excessive quantities of cystine is not the only abnormality exhibited by cystinurics. Leucin and tyrosine have sometimes been found in company with cystine. The presence of an excess of cystine in the urine may not be an isolated phenomenon but merely one manifestation of an error of metabolism which also involves other primary protein fractions.

Clinical Picture

Cystinuria only causes symptoms because of the passage of crystals or the formation of calculi. Cystine calculi have been said to develop in about 2 per cent. of cystinurics, but since cystinuria without lithiasis is so frequently overlooked this figure cannot be much more than a guess. When symptoms appear they resemble those of other forms of calculous disease, namely frequency and pain followed by haematuria. Patients belonging to known cystinuric families naturally seek medical advice fairly early, but those unaware of their abnormality often procrastinate. Symptoms may begin in infancy or at any age in adult life. Children with symptoms of cystine lithiasis are often pale and undernourished, but adults are

usually in relatively good health. Cystinuria should be kept in mind as a possible diagnosis in all cases of calculous disease in children, and in adults wherever there is a suggestive family history.

Two clinical characteristics of cystine lithiasis deserve special mention. The first is that the urine is generally sterile even when large calculi have formed in the kidney, and it would seem that the factor of infection plays only a minor rôle in causing calculi amongst cystinurics. The second peculiarity of cystine lithiasis is that the renal stones are often unilateral, a point of great importance in relation to surgical treatment. The limitation of the disease to one side only may be determined by the existence of an abnormality in the affected kidney, resulting in defective drainage and retention of crystals. Or it may be that cystine excretion may not be equal on both sides. Few comparisons of cystine excretion have been made in urine collected from each kidney by catheterizing the ureters, but in a remarkable case recorded by Melvin and Andrews (1937) the drainage from the right kidney was compared with the urine collected through the urinary bladder from the other kidney. The drainage from the damaged kidney contained no cystine, although other urinary constituents were normal in amount. Later, after the incision had been closed, separate catheterization of the two ureters produced urine samples containing comparable amounts of cystine. Seven weeks later the ureteric catheterization was repeated and this time again the cystine excretion was unequal, the higher concentration being found in the kidney from which the stone had been removed.

Diagnosis

The diagnosis of cystinuria is established either by finding crystals by microscopic examination or proving by chemical tests that there is an excessive secretion of cystine in the urine.

Microscopic examination

Cystine crystals are easily seen in the centrifuged deposit of the urine, using either the one-sixth or two-thirds objective of the microscope; they appear as colourless hexagonal plates, and are only likely to be found in an acid urine. The crystals are soluble in ammonia, alkalis and hydrochloric acid, but are insoluble in water, acetic acid, alcohol and ether. Hexagonal crystals of uric acid may sometimes be mistaken for cystine but, unlike cystine, uric acid crystals do not dissolve in dilute mineral acids. The distinction between crystals of cystine and uric acid is most easily made as follows:

Transfer a drop of the urine deposit on to a microscope slide beneath a coverslip and focus

with the one-sixth objective. Place a drop of 30 per cent. hydrochloric acid at the edge of the coverslip and draw through with blotting paper at the opposite edge. Cystine crystals dissolve in the hydrochloric acid but uric acid crystals do not.

Chemical Tests

In cases of suspected cystinuria in which the typical hexagonal crystals of cystine have been found, the urine may be tested for excess of cystine as follows:

Cyanide Nitroprusside Test

The urine is treated with sodium cyanide (5 per cent. NaCN in N/NaOH) to reduce cystine to cysteine, and after the reduction has proceeded (about 10 minutes) a few drops of sodium nitroprusside are added. In the presence of cystine a magenta colour is developed, whereas normal urine shows only a faint brownish colour.

Cystine calculi are fawn coloured or light green when first removed, but after exposure to light the colour gradually deepens. The outer surface is smooth or slightly mammilated and feels waxy. On section they have a slightly translucent appearance and the cut surface does not show concentric laminations. They assume different shapes according to the cavity in which they form.

Cystine calculi can easily be crushed in a mortar the powder burns with a blue flame causing a sharp pungent smell. The presence of cystine can be confirmed chemically by dissolving the powder in concentrated ammonia and allowing it to evaporate when typical hexagonal crystals of cystine separate out.

Radiological Diagnosis of Cystine Calculi

Cystine calculi can generally be quite easily demonstrated by X-rays. They are slightly more opaque than pure uric acid and phosphate stones. Renander (1937) states that a cystine calculus in the kidney with a diameter of 3 cm. produces a shadow about 300 times as dense as the soft tissue in the neighbourhood.

Treatment

In considering the treatment of cystinuria the distinction should be made between (1) cystinurics who merely excrete an excess of cystine but whose urine is free from crystals; (2) cystinurics who pass crystals but have no signs or symptoms of urinary calculi, and (3) cystinurics who have formed urinary calculi.

(1) Cystinurics who do not pass cystine crystals but who simply excrete an excess of cystine require no medical treatment, but they should be advised to drink plenty of fluids, to avoid a high protein diet and to have a specimen of urine examined oc-

casionaly for crystals. If no crystals are found in an acid specimen of urine of an average specific gravity then the abnormality may be neglected.

(2) Cystinurics who habitually pass crystals should be advised to keep the urine dilute by large fluid intake, and to live on a vegetarian or a low-protein diet. The crystals can generally be made to disappear from the urine if sufficient alkali is given by the mouth, but the amount required is likely to be greater than a patient could tolerate for more than a short spell. Anyhow, prolonged alkalization is not necessary because most cystinurics who are careful about their diet and fluid intake succeed in avoiding calculous disease.

(3) Once renal calculi have formed surgical treatment is necessary. Fortunately the disease is often unilateral and the patients are in good condition for operation. After surgical removal of a cystine calculus another may form later in the kidney, so the patient needs to be kept under

supervision. Cawker (1946) advises that after removal of cystine calculi from the kidney recurrence may be avoided by adopting, for one week in each month, a low protein diet with sufficient alkali by mouth to keep the urine alkaline. He says that this not only prevents crystallization of cystine but will actually dissolve a small cystine calculus. This is worth trying, but there is little evidence that cystine calculi can be dissolved by keeping the urine alkaline. Alkalinization of the urine merely prevents the deposition of crystals; it does not diminish the excretion of cystine nor dissolve stones which have already formed.

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THE RIDDLE OF GENERAL PRACTICE

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General practice has been brought into the forefront of medical politics (and I am extremely glad that this has happened) by, without question, the publication of the Collins' Report and two B.M.A. Reports, the one on the training of the general practitioner and the other on health centres. Collins, as you know, was an individual from the colonies investigating alone and at the request of the Nuffield Foundation. He describes in a long report of 40,000 words his surprise and distress at what he saw, wondering in his more pessimistic moments whether the sinking ship which was general practice was capable or even worthy of salvation, and finally concluding that it was and that it must be saved. The B.M.A. Committee on general practice and the training of general practitioners consisted of 32 members of which, as far as I could make out, not more than one-third were general practitioners. It sought to plot the path from the 'Slough of Despond' in which it found general practice forward to the 'Delectable Mountains.'

The Collins' Report filled me with the utmost gloom partly because of its conclusions, and partly because those conclusions were so sincerely held. My mind went back to Brett Young's descriptions

of industrial practice before the 1913 Act, in such books as 'Dr. Bradley Remembers' or 'Brother Jonathan,' and it appeared from the conclusions of the report that what was true then remains true to this day and with even heavier emphasis. That his standard of what is good practice and what is bad was not my own had nothing to do with my gloom; it was the widespread degradation of medicine that he depicted which was as shocking as it was incredible. The report is not true of innumerable general practices any more than Cronin's 'The Citadel' depicts accurately the average inhabitants of Harley Street.

The B.M.A. Committee's Report on general practice and the training of the general practitioner produced an entirely different impact. I was reminded of the Pilgrim's progress as he journeyed to the Celestial City and of all the trials and tribulations through which he had to pass before he arrived at that desired haven. Much of it I felt to be unpractical and idealistic in a severely practical and far from ideal world. I wondered much if the gentlemen of the B.M.A. could not have plotted a simpler path and envisaged a simpler traveller.

The report on health centres was to me infinitely