

AMINO-ACIDURIA IN GALACTOSAEMIA

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During recent years the condition of galactosaemia has been recognized more frequently, but the total number of cases recorded in paediatric literature is still very small. Much interest has been aroused by this rare metabolic disorder because of the satisfactory results following appropriate treatment and because of the serious consequences of misinterpreting the clinical picture. Although diagnosis and treatment are now on a firm basis, the pathogenesis and the nature of the metabolic derangement are not yet fully understood.

Two Recent Cases

During the past four months two infants have been observed who presented the classical symptoms and signs of vomiting, failure to thrive, transient jaundice, enlargement of the liver, and frequent loose stools. One,

who has been studied from the first days of life, developed central polar cataracts at the age of 4 weeks; these have subsequently regressed. Examination of the urine in each case showed the presence of a reducing substance which was identified both chemically and by chromatography as galactose. The galactose-tolerance tests in both infants were grossly abnormal, showing an initial galactosaemia, a steep rise of the galactose blood levels, and a slow fall over several hours.

Further evidence supporting the diagnosis was obtained by the therapeutic test of omitting milk from the diet; this produced definite improvement in the infants' condition and led to the disappearance of galactose from the urine.

Because of the hepatomegaly in the first infant the possibility of an amino-aciduria as a result of liver damage was considered and studies of the urine were undertaken. Because of the unusual findings these studies were repeated with the second infant.

Urine Chromatography

One-way paper chromatograms were made on as many specimens of urine as possible, the volume of urine containing 250 μ g. of total nitrogen being taken for each analysis. Both cases consistently showed an excessive amino-aciduria when on a milk diet but not when on a diet from which milk was entirely absent. The picture reappeared when 2 g. of galactose a day was added to the milk-free feeds. It also followed a galactose-tolerance test.

In order to identify the amino-acids more definitely two-way chromatograms were made on urines selected on the basis of the one-way chromatography, using phenol/collidine and phenol/tetrahydro furfural alcohol as pairs of solvents and again taking the volume of urine containing 250 μ g. of nitrogen. These chromatograms confirmed the previous findings and allowed of a provisional identification of all the amino-acids present. The details of the amino-acid pattern were similar in both cases. Descriptive diagrams of two chromatograms of the urine in each case are shown in Figs. 1, 2, 3, and 4. The amino-acid spots are shown in their usual positions on an actual chromatogram. They are drawn in the form of circles, the relative sizes of the circles giving some indication of the strength of ninhydrin colour and hence of the quantity of each amino-acid present. The urine is assumed to have been placed at the right-hand bottom corner. Phenol has been run as first solvent from right to left followed by collidine in an upward direction.

It can be seen that on the milk diets a definite amino-aciduria was present, involving a large number of amino-acids. A two-way chromatogram of the first case after the administration of galactose showed practically the same pattern as the original urine. It was noted that the pattern obtained was different from any pattern seen in cases of extensive liver damage in infants of the same age.

Chromatographic Report

It was felt that confirmation of the amino-acid pattern should be obtained, and Dr. Dent, of University College Hospital, kindly examined specimens. He reported as follows: "Review

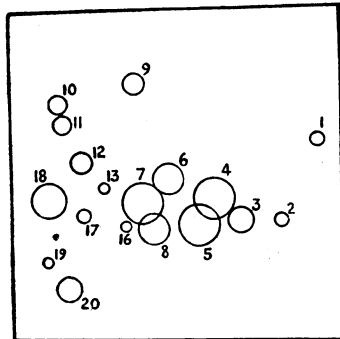


FIG. 1.—Urine of Case 1 while on a milk diet. Note the large number of amino-acids, some of them in large quantities.

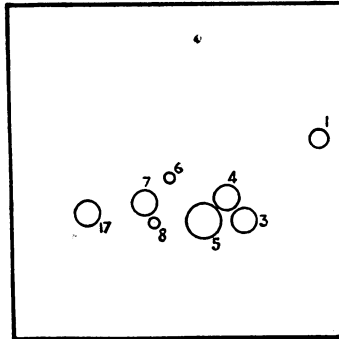


FIG. 2.—Urine of Case 1. After four days on a milk-free diet. All the amino-acids have decreased in quantity—some have disappeared altogether. The excretion is still, however, slightly abnormal.

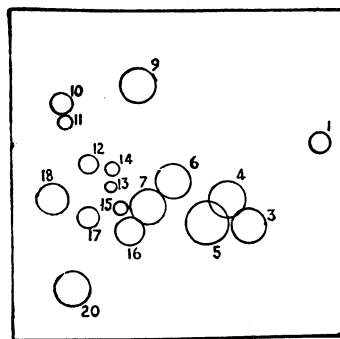


FIG. 3.—Urine of Case 2 while still on a milk-containing diet. The characteristics of the amino-aciduria are very similar to those shown by Case 1.

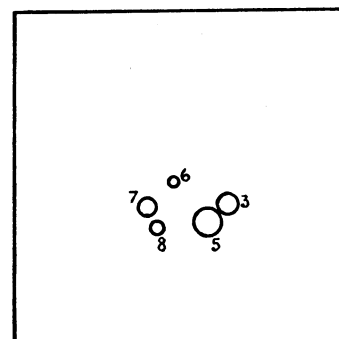


FIG. 4.—Urine of Case 2 on a milk-free diet.

Identification of Spots.—1, Cystic acid (from cystine); 2, aspartic acid; 3, glutamic acid; 4, serine; 5, glycine; 6, threonine; 7, alanine; 8, glutamine; 9, tyrosine; 10, phenylalanine; 11, leucine; 12, valine; 13, alpha-amino-*n*-butyric acid; 14, methionine sulphone (from methionine); 15, histidine; 16, citrulline; 17, beta-amino-*iso*-butyric acid; 18, methyl histidine; 19, arginine; 20, lysine.

of all the chromatograms leaves no question that there is a gross amino-aciduria associated with the galactosuria, which rapidly becomes more normal under treatment with the milk-free diet. The especially unusual characteristics (as against those of the already known amino-acidurias) are the disproportionately large quantities of serine, threonine, methyl histidine, lysine, and tyrosine. It could be that this pattern is specific for the disease. Of especial interest is the fact that the common liver diseases, so far as they have been investigated, display urine amino-acid patterns quite different from those shown by these two cases (Dent and Walshe, 1951). On the other hand, the pattern shows some resemblance to that occurring in the renal amino-acidurias, especially that of Wilson's disease."

Discussion

Pathological excretion of amino-acids in urine has recently been reviewed by Dent (1950, 1951), and it appears that there are two possible mechanisms by which this may occur. The first is the "overflow" mechanism whereby the excretion is the result of a raised plasma level; this occurs to varying extents in both acute and chronic liver disease and in phenylketonuria. The second is a true "renal" mechanism whereby the excretion occurs in the presence of normal plasma levels, presumably as the result of a lowered kidney threshold—that is, raised clearance; this occurs in cystinuria, in the Fanconi syndrome, and in Wilson's disease, all of which have a genetic background. There is also an acquired form of renal amino-aciduria which occurs occasionally as the result of the action of poisons such as lead and uranium on the renal tubules.

No reports have as yet appeared in which a disorder of amino-acid metabolism has been implicated in galactosaemia, but it is possible that this amino-aciduria may be specific and an expression of a "renal" mechanism.

It is hoped to publish the results of further work on these lines in the near future.

We are grateful to Dr. C. E. Dent and his assistant, Miss Dorothy Fowler (University College Hospital Medical School), for their generous help with the sugar and amino-acid chromatography and its interpretation; to Miss Jean Summerscales for her assistance in the chemical identification of the galactose; and to Professor Wilfrid Gaisford for his interest and criticisms.

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The Central Council for the Care of Cripples recently produced a *Summary of Legislation and Directory of Organizations for the Care of the Physically Handicapped* (Heinemann Medical Books, price 5s. 6d.), which, in spite of its unwieldy title, is a useful little book of over 100 pages which should be close to the hand of everyone, medical or lay, concerned in the treatment and care of the disabled or crippled. The addresses and functions of many local voluntary societies are included, as well as clear summaries of the provisions of the National Assistance and National Health Service Acts, and other forms of Government aid. There is also a section on the training of orthopaedic nurses and welfare workers as well as of the handicapped themselves.

EXTENSIVE RESECTION OF THE SMALL INTESTINE

A SHORT REVIEW, WITH TWO NEW CASES

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Resection of a large part of the small intestine is called for infrequently and usually unexpectedly. The occasion may be an emergency operation for adhesion obstruction, strangulated hernia, mesenteric vascular occlusion, or mesenteric injury. Less often the indication is widespread tuberculous or other disease of the small intestine, while occasionally it is malignant disease or a benign tumour involving the mesentery. In any case, the need for so drastic an operation has seldom been foreseen and a decision has to be made on the spot. Textbooks on operative surgery give little information, and although many articles on this subject have been published it is still not easy to find out what risk there is of serious impairment of health after an extensive resection. The satisfactory results in the two cases here reported and a review of some of the literature have considerably increased my optimism with regard to this operation.

Extent of Removal

It is true that in most cases the amount of bowel removed is decided by the disease rather than by the surgeon, but even in these there is sometimes room for judgment in deciding whether an extra foot or two of bowel is better removed or left behind. In a minority of cases the extent of removal is far more a matter for individual opinion. The surgeon's decision on how far he should jeopardize the patient's future health by increasing the scope of the operation must be based on his knowledge of the likely effects of removing a large part of the small bowel. If they were to be almost inevitable chronic invalidism, diarrhoea, and misery, then he would serve his patient best by conserving as much as possible. If he knew that several feet more or less would make little difference as regards future health, he would plan the operation accordingly, for long resections are no more difficult or dangerous than short ones.

The case records surveyed support the view that resections of up to one-half of the small intestine are not followed by serious metabolic disturbance. When they exceed three-quarters, then serious metabolic disturbance is probable but by no means certain. There is no clear indication whether resection from the proximal or the distal end is likely to have the greater effect. In practice most massive resections are distal, and the bowel remaining is jejunum. This would be expected from a consideration of the blood supply, as well as from the greater liability of the distal bowel to disease generally and to gangrene from mechanical causes.

A resection of 6 ft. (1.8 m.) is taken by most authors as the minimum qualifying for the term extensive or massive. When less than this is removed the problem of later metabolic upset, in the absence of other disease, never seems to arise. One patient of Jerauld and Washburn's (1929) had only 6 ft. (1.8 m.) resected for polyposis and later had diarrhoea after milk or anything containing fat, but there may well have been polyposis of the