CONGENITAL ABNORMALITIES OF AMINO ACID TRANSPORT IN RENAL TUBULES

By Charles U. Lowe, M.D.
Statler Research Laboratories of the Children's Hospital, Buffalo, and the Department of Pediatrics, the University of Buffalo School of Medicine

Varieties of syndromes have been described in which an abnormal amount of organic acid appears in the urine. In many of those syndromes which have been carefully studied, amino acids appear to constitute the major portion of organic acids. This probably is the result of the development of adequate methodology for the determination of amino acids. Nevertheless, the author proposes classifying these diseases as organic acidurias, since it is his belief that there are organic acids, other than amino acid, present in the urine of these patients.

Although the central theme of the Symposium of which this paper is a part is genetic defects, in the classification which is to be presented for consideration, some syndromes are included which are not genetic in origin. This is done for the purpose of completeness and to suggest the relationships between the syndromes with a genetic background and those in which the organic aciduria results from some nongenetically controlled aberrations.

These syndromes may be roughly divided into two groups: Those in which the concentration of amino acids in the blood is elevated and those in which it is normal. The problem of classification of these syndromes has recently been reviewed in detail.1,2 In the group of syndromes with normal concentrations in the blood, further subdivision is necessary into four apparently different groups. In Table I are listed the diseases falling into these various categories.

Among the diseases characterized by elevated concentration of organic acids in the blood, one may observe that only phenylpyruvic oligophrenia represents a congenital anomaly. This has been discussed in detail in this Symposium in a lucid exposition presented by Dr. Meister. The other syndromes in this classification are clearly beyond the scope of a symposium on a genetically determined illness.

It is also clear that none of the syndromes resulting from renal intoxication (group IIa, Table I) are within the scope of this Symposium since in no instance do these represent genetically controlled disease. The diseases in group IIb include a host of syndromes which are of great interest to both geneticists and biochemists. These all appear to be genetically controlled in that, in all cases, there are many more examples of the disease within families than among the general population.

Cystine-lysinuria is a syndrome characterized by the appearance in the urine of abnormally large amounts of cystine, lysine and ornithine. On the basis of experiments in which cystine and cysteine were fed to both normal subjects and those with cystinuria, it was proposed that this disease resulted from an aberration in the metabolism of protein.3,4 It is clear, however, as a result of recent observations, that this interpretation is incorrect.5 The abnormality is entirely renal in origin, and the finding of organic acids in the urine results from impaired tubular reabsorption of the involved amino acids. In fact, the clearance of cystine is equal to the glomerular filtration rate.6

H-syndrome or Hartnup syndrome is a distinct entity recently described by Dent and associates.7 It is characterized by the appearance in the urine of a variety of amino acids, but what is of particular interest to the pediatrician and geneticist is...
TABLE I
CLASSIFICATION OF DISEASES WITH ORGANIC-ACIDURIA

I. Concentration of Organic Acids in the Blood is Elevated—No evidence of renal abnormality:
   - Celiac disease
   - Liver disease
   - Phenylpyruvic oligophrenia
   - Vitamin C deficiency
   - Prematurity
   - Thiamine deficiency

II. Concentration of Organic Acids in the Blood is Normal—Kidney normal or abnormal:
   a. Toxic
      - Lead poisoning
      - Uranium ingestion
      - Lysol® (phenol) intoxication
      - Total body x-radiation
      - Severe burns
      - Excess vitamin D
      - Nephrosis

   b. Genetic defects
      - Cystine-lysinuria
      - H-syndrome
      - Infantile de Toni syndrome
      - Milkman's syndrome
      - Vitamin D resistant rickets
      - Buphthalmos and organic aciduria
      - Pyruvic aciduria with steatorrhea
      - Luder and Sheldon syndrome
      - Tyrosinosis
      - Acaecetonuria

   c. Genetic defect producing "toxin"
      - Wilson's hepatolenticular degeneration
      - Cystinosis
      - Galactosemia

   d. Substance essential for renal function absent
      - Vitamin D deficiency

In the original descriptions of vitamin D-resistant rickets, it was suggested that the disease resulted from refractoriness of the end-organ to an amount of vitamin D sufficient in normal patients to promote normal growth of bone. No progress in the understanding of the pathogenesis of this disease was made until Jonxis demonstrated that amino-aciduria was also present in individuals with this syndrome. It would appear that the urinary findings are similar to those observed in patients with vitamin D-deficient rickets. The amino-aciduria is characterized by an excessively large amount of glycine, although other amino acids are present in abnormal amounts. The administration of vitamin D
in amounts sufficient to cause healing of bone decreases the amino-aciduria but never results in a lowering to normal amounts. On the basis of the report by Ayer et al., it is not surprising that hyperphosphaturia and glycinuria appear in the same syndrome, since it has been suggested that these substances share a common transfer mechanism in the renal tubules. The relationships between these syndromes and vitamin D-deficient rickets will be discussed later.

The syndrome of buphthalmos and organic-aciduria is unique in at least one respect—its characterized by a specific anatomic abnormality in association with an abnormality in urine constituents. Children with this disease are born with glaucoma (probably as a result of defective development in the canal of Schlemm), severe mental retardation, systemic acidosis and an organic-aciduria in which only a fraction of the organic acids can be accounted for by the determined amino acids. A single child with pyruvic-aciduria and steatorrhea has been reported from the author’s laboratory; this patient was studied only because he appeared similar, in many respects, to the children with buphthalmos and amino-aciduria (although the glaucoma was missing), with the hope of identifying the other organic acids. The discussion will return to this problem subsequently.

The syndrome of Luder and Sheldon has been recently described. It is clearly familial in nature, and represents a type of amino-aciduria, although the pathogenesis of the aberrations is not clear. It may result from a specific defect in hydrogen-ion transfer in association with amino-aciduria.

The literature contains but a single description of an individual with tyrosinosis, and its rarity probably precludes the necessity of further discussion at this time. Alcaptonuria, a genetic defect, has been carefully studied and, on the basis of available knowledge, appears to be both a renal and metabolic defect.

Three syndromes appear to fall into the group of diseases which are characterized by a genetic defect producing a toxin which, in turn, affects organic-aciduria (group IIc, Table I). Wilson’s hepatolenticular degeneration has been discussed by Dr. Gitlin in another paper in this Symposium. It seems clear that a defect in copper metabolism exists in this disease. The important point with respect to renal function is that copper accumulates in the tissue of these patients in spite of, or because of, the fact that the mechanism of copper transport in the plasma is abnormal. The result appears to be an intoxication of the kidney with resulting impairment of function. These patients have amino-aciduria and, apparently, occasionally glucosuria. No defects in bone structure resulting from rickets or osteomalacia have been described.

Cystinosis, we have suggested, should be synonymous with the Fanconi syndrome. It is proposed that those patients with amino-aciduria, systemic acidosis and cystine deposits in the parenchymatous organs of the body be separated from the individuals with what we have designated the infantile De Toni syndrome. Cystinosis appears to be different from the infantile De Toni syndrome in that glucosuria is not a constant finding in the former condition and in the fact that almost without exception the disease is fatal in childhood in the absence of therapy. Cystine crystals have been observed in the cornea by slit lamp examination and in the lymph nodes, liver, spleen, etc., upon microscopic examination. The administration of large amounts of vitamin D (50,000 to 100,000 units per day), along with alkalizing salts, promotes healing of the bone lesions and, for a reason which is far from clear, causes a significant decrease in the amino-aciduria. Even more confusing is the observation of Freudenberg that large amounts of adenylic acid can diminish the amino-aciduria. The inclusion of cystinosis in category IIc (Table I) is justified only if the assumption is made that the accumulation of cystine crystals in the kidney are the cause of the amino-aciduria. Certainly
it is clear that amino-aciduria can occur in the absence of renal cystinosis.

Galactosemia is a third example of a disease in which an accumulation of a toxic substance produces aberrations in renal function.\textsuperscript{32, 33} In this case, the evidence of intoxication is more obvious, since it is possible in these patients to induce amino-aciduria by administration of galactose and cure the aberration by a diet which is free of galactose.\textsuperscript{34, 35} Apparently, the fundamental enzymatic defect causing galactosemia\textsuperscript{36, 37} does not per se cause amino-aciduria, since maintenance on a galactose-free diet in no way alters the genetic enzymatic abnormality.

In the final group (IIc, Table I), organic-aciduria in which some substance essential for renal function is absent, we have so far a single entity: vitamin D-deficient rickets. As mentioned previously, in this condition as in vitamin D-resistant rickets, amino-aciduria exists. Whereas we do not commonly consider this an hereditary symptom, it appears possible, on the basis of reports by Jonxis\textsuperscript{12, 13, 38} that an hereditary rachitic diathesis produces individuals with increased requirement for vitamin D.

In a survey of patients with vitamin D-deficient rickets, Jonxis observed that an amino-aciduria was uniformly present and that glycine was present in greatest amount, a situation which appears to be unique among the amino-acidurias. The administration of vitamin D caused a substantial decrease in amino-aciduria. There were certain patients who did not have vitamin D-resistant rickets (based upon the dose of vitamin D required to cure the rickets) in whom the amino-aciduria persisted at a level higher than that found in normal subjects. When vitamin D in curative doses was given to these patients, the rickets healed, but amino-aciduria persisted. When members of the families of such patients were examined, it was apparent that certain individuals, although without rickets, had abnormal amino-aciduria.

This suggests that there may be all gradations of vitamin D resistance or requirement. Overt examples are those patients who appear in a clinic as vitamin D-resistant rickets, and the most subtle examples being those with a persistent, although mild, amino-aciduria and a rachitic diathesis. This concept of gradation in vitamin D requirement may gain support from the observation that individuals with vitamin D-resistant rickets have great variation in the amount of vitamin D required to cure the rickets.

**DISCUSSION**

Is it possible to relate these syndromes in any way, and are there common aspects to all patients with amino-aciduria? One can suggest certain interrelations (Fig. 1), although these interrelations may apply to only a limited number of examples of syndromes with amino-aciduria (groups IIc and d, Table I). Several years ago, Berliner and his co-workers demonstrated that when maleic acid was infused into acidotic dogs, the urine promptly became alkaline and the phosphate excretion increased.\textsuperscript{39} These experiments were of short duration (6 hours), and during this period there was no significant excretion of organic acids in the urine. It was suggested by these authors that maleic acid interfered, in a competitive way, with the conversion of fumaric acid to succinic acid, since maleic acid is a stereoisomer of fumaric acid. On an enzymatic basis, this implies interference with the action of succinic dehydrogenase in the Krebs dicarboxylic acid cycle; hence, with aerobic glycolysis. Subsequently, Harrison administered maleic acid to rachitic rats and observed not only an increase in phosphate in the urine but also amino-aciduria and glucosuria.\textsuperscript{40} Hence, the rats developed a syndrome similar, in many respects, to the organic-acidurias seen clinically.

These observations indicate that when aerobic glycolysis is compromised, tubular reabsorption of hydrogen ions, glucose, phosphate and amino acids may be impaired. The problem is made even more interesting by the observation that the incubation of maleic acid with liver slices
produces specific inhibition of succinic dehydrogenase. Incubation of slices with oxidized glutathione causes similar inhibition which is reversed by the addition of reduced glutathione.41

When copper in minute amounts is incubated with succinic dehydrogenase, it too causes interference with the conversion of fumaric to succinic acid, and again, the introduction of reduced glutathione reversed the inhibition.42 This suggests not only a relationship between the amino-aciduria of Wilson’s disease and that found in other examples of organic-aciduria but also implies that, if an individual with Wilson’s disease can be “decoppered,” the amino-aciduria should disappear. Recent observation has indicated that this is, indeed, the case.43

Finally, Conn44 reported that, when adrenocorticotropic (ACTH) or cortisone was administered to normal subjects, amino-aciduria and glucosuria resulted. The studies suggested that the abnormal urine constituents resulted from an abnormality in renal function and not an elevation in plasma concentrations. At the same time, the serum concentration of oxidized glutathione decreased. When an infusion of reduced glutathione was begun, the amino-aciduria and glucosuria promptly disappeared.

These data, as a group, indicate the possibility that interference with aerobic glycolysis may produce specific renal disabilities. It might be attractive to speculate that, if interference with aerobic glycolysis was actually the cause of these syndromes and if the interference was of the nature of a block in the Krebs cycle, one might find increased amounts in the urine of those organic acids which are involved in the Krebs cycle.

Is there any evidence to support this hypothesis? A brief reconsideration may be given to the patients with buphthalmos and
TABLE II

<table>
<thead>
<tr>
<th>Disease</th>
<th>PO₄</th>
<th>Glucose</th>
<th>Amino Acids</th>
<th>H⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactosemia</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rickets</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>-</td>
<td>?</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Maleic acid</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

amino-aciduria, and to the single individual observed with pyruvic-aciduria and steatorrhea. As mentioned previously, in the children with buphthalmos and amino-aciduria, only a portion of the organic acids in the urine were accounted for when amino acids were determined. It was not possible at the time these patients were under study to determine the nature of the other organic acids. When, however, the child with pyruvic-aciduria and steatorrhea appeared, a brief opportunity was available, prior to his death, to examine the urine. It was found that there was a considerable increase in two of the acids of the Krebs cycle, namely, citric acid and oxalacetic acid, as well as two acids, pyruvic and lactic, not specifically a part of the Krebs cycle but the presence of which indicated interference with aerobic glycolysis.

These observations suggest that further examination of urine in appropriate subjects may reveal the presence of other acids of the Krebs cycle, but they cannot be construed to imply that all aberrations in renal tubular function can be explained simply by inhibition of succinic dehydrogenase. Examination of Table II indicates that, in many of the syndromes, the renal tubular dysfunctions are more specific than those which occur following administration of maleate. It is conceivable that these syndromes differ either in the degree of inhibition of aerobic glycolysis or, alternatively, that different enzymes in the Krebs cycle are affected in each syndrome. It seems reasonable to suggest that this would be a fruitful area for further investigation.

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