The Renal Aminoacidurias

Harold A. Harper and Paul D. Doolan*

The finding of increased amounts of amino acids in the urine is characteristic of several inherited as well as acquired metabolic diseases. Such aminoacidurias are usually classified as "overflow" or "renal" in origin. In the former instance, it is assumed that the concentrations of amino acids in the plasma markedly exceed the capacity of the normal renal tubule to reabsorb completely the filtered load of amino acids. In all such cases, the quantities of amino acids in the plasma will be found to be in excess of the normal. Examples of such "overflow" aminoacidurias are those found in far-advanced liver disease and also in phenylketonuria. However, the majority of aminoacidurias of clinical interest are of the renal type, in which, even with normal concentrations of amino acids in the plasma and, consequently, normal filtered loads in the kidneys, there are increased amounts of amino acids excreted into the urine. Under these circumstances the cause of the aminoaciduria is attributed to a decreased capacity of the renal tubule to reabsorb amino acids. To appreciate fully the significance of a renal aminoaciduria, it is necessary to review the normal mechanisms whereby the renal tubule handles amino acids. Failure to do so has led to erroneous interpretation of the results of analysis for amino acids in the urine.

Normal Renal Reabsorption of Amino Acids

In normal subjects under fasting conditions, there is almost complete reabsorption of all of the amino acids filtered at the renal glo-

*Present address: Naval Medical Research Institute, Bethesda, Md.
merulus. If a mixture of amino acids is infused intravenously so that the filtered load is increased, then both the amounts of amino acid excreted and those reabsorbed are increased. As a result, it would be expected that the attainment of a maximum tubular reabsorptive capacity (Tm) would be gradual. A Tm has been demonstrated for certain amino acids in the dog \((1)\), but attempts to do so in the human were unsuccessful. In the experiments of Doolan et al. \((2)\), it was believed that it might be possible to reach a Tm for glycine in the normal human subject. For this purpose the amino acid was infused intravenously at rapid rates to increase the filtered load. Although there were indications of an approaching Tm, the toxicity of the amino acid at such high plasma levels made it necessary to terminate the experiment before a Tm could be established.

There is evidence for competition for reabsorption between certain groups of amino acids such that a high filtered load of certain amino acids presented to the tubule for reabsorption may increase the excretion into the urine of other amino acids. An example is the effect of a high filtered load of lysine to increase the excretion of cystine \((3)\).

The pattern of amino acids in the urine does not resemble that of the plasma. Thus it is clear that the renal tubule exhibits selectivity with respect to the reabsorption of each of the amino acids presented to it. Endogenous clearances of individual amino acids in humans were found by Doolan et al. to range from a low of 0.12 ml./min. for valine to highs of 5.12 for glycine and 6.38 for histidine \((4)\). It is evident from these data that reabsorption of amino acids by the renal tubule is normally in excess of 93% of the filtered load. This is so even after intravenous infusion of free amino acids at a rate approximating that used clinically. Under these circumstances, the total amount of amino acid nitrogen excreted represents less than 4% of that given \((4)\). Despite definite and in some instances marked elevations in serum concentrations, only five naturally occurring amino acids were ever excreted at a rate exceeding 0.5 mg./min., namely, glycine, histidine, serine, threonine, and occasionally lysine.

The reabsorption of amino acids by the renal tubule is thought to be a process of active transport involving a mechanism of a highly selective type. This idea is supported by the fact that the efficiency of reabsorption of the naturally occurring \(L\) isomer of an amino acid is much greater than that of the \(D\) isomer of the same amino acid \((5)\). The observation that a significant increase in clearance of the \(D\) form follows a diuresis induced by a water load is taken as consistent with the
notion that the D forms are either passive participants in or committed to a different transport mechanism than that associated with the natural L form. Differences in rates of transport of D and L forms of amino acids have also been shown to be characteristic of the intestinal epithelium and of the human placenta (6).

From what has been stated above, it should be apparent that the excretion of amino acids is normally influenced by the glomerular filtration rate, even when the plasma concentrations of amino acids are normal. If one is interested in establishing that an aminoaciduria is of the renal type, that is, attributable to a renal tubular defect, it thus becomes necessary to take the glomerular filtration rate into account. An example of the importance of this fact is to be found in the circumstances which surround the apparent aminoaciduria of normal pregnancy. In this connection, a histidinuria has attracted the most attention, presumably because histidine is normally cleared in comparatively large amounts and therefore can be readily detected even by a colorimetric method. In fact, the so-called histidinuria of pregnancy is so characteristic that it was proposed as a chemical test for pregnancy (7) at a time when the modern tests had not been devised. It was further observed that the expected histidinuria disappeared in pregnant subjects with preeclampsia. It would be expected that various metabolic causes not involving simple renal mechanisms would be invoked to explain these phenomena. Particularly attractive because of the absence of the normal histidinuria was the idea that an abnormality in histidine metabolism, perhaps involving excess formation of histamine, was involved in the etiology of the preeclamptic state.

Studies of renal clearance of histidine in normal pregnancy and in pregnant subjects with preeclampsia by Page et al. (8,9) revealed that in normal pregnant women, the rate of glomerular filtration increased from a nonpregnant mean of 104 to a pregnancy mean of 171 ml. per minute per 1.73 sq. M. of body surface. It was this change in glomerular filtration rate, aside from any change in tubular reabsorption or decrease in rate of metabolism of histidine, that accounted for about half of the excess histidine excreted. In contrast, in the preeclamptic patients, there was a marked diminution in glomerular filtration rate that was largely responsible for the decreased excretion of histidine.

It should be obvious that the existence of an aminoaciduria may be overlooked in patients with a marked decline in glomerular filtration rate as indicated by uremia and as conveniently measured by creati-
nine clearance. An important illustration of this situation is to be found in following the course of a young patient with the generalized aminoaciduria and other renal tubular defects of the Fanconi syndrome. Early in the course of the disease, when the glomerular filtration rate is still relatively normal, the generalized aminoaciduria, which is due to a renal tubular reabsorptive defect, is readily apparent. However, as the disease progresses over a period of several years, it will be noted that the excess excretion of amino acids in the urine declines to normal. This is concurrent with a reduction in the glomerular filtration rate, as evidenced by a rising blood urea nitrogen and other signs of uremia. Indeed, in these patients, shortly before death occurs as a result of renal failure, there may no longer be any evidence of significant aminoaciduria. It follows that if such a patient were to be studied for the first time at this late stage of the disease, a negative diagnosis of generalized aminoaciduria would be forthcoming.

**Diseases Associated with Aminoaciduria**

With the above facts concerning the renal handling of amino acids in mind, we may now turn to a consideration of some of the specific diseases in which a renal aminoaciduria is an associated biochemical finding. In some instances the aminoaciduria is generalized, that is, increased excretion of all of the amino acids occurring in the plasma can be detected. In other instances, the aminoaciduria is more specific in that there are increased amounts of some amino acids in the urine while all others are excreted in normal amounts. It should also be noted that the aminoacidurias may result from an inherited metabolic abnormality, in which case the aminoaciduria is a permanent finding, or it may be an acquired abnormality which may either be transient or become permanent. Examples of transient aminoacidurias are those reported as occurring during the diuretic phase after acute renal insufficiency, or as a result of a deficiency of potassium. Aminoacidurias of longer duration occur as a result of poisoning with heavy metals, particularly cadmium and uranium, but also with lead or mercury. The aminoaciduria often found in patients with Wilson’s disease may also be included here because it appears to be associated with the toxic effect on the renal tubule of copper, which characteristically accumulates in patients with this disease. Generalized aminoacidurias are also occasionally found in association with the nephrotic syndrome (10,11) and with multiple myeloma (12,13).
Fanconi Syndrome

The Fanconi syndrome is perhaps the most frequently studied among the genetically transmitted aminoacidurias (14). The syndrome as recognized in infants and children is characterized not only by a generalized aminoaciduria but also by other renal tubular defects affecting reabsorption of phosphate and glucose, and frequently also the renal handling of potassium and water, as well as the secretion of hydrogen ions and the manufacture of ammonia. The aminoaciduria itself, although generalized, is quantitatively minimal and is therefore of no metabolic consequence. This is in contrast to the significance of the other tubular abnormalities. Thus, the persistent phosphate leak engenders a negative phosphorus balance and resultant impairment of development of bone, as evidenced by the occurrence of rickets. The serum phosphate is generally lower than normal, and vitamin D in ordinary dosages is therapeutically ineffective. This form of renal rickets is in consequence often described as hypophosphatemic or vitamin D-resistant rickets. The other associated renal tubular abnormalities affecting the handling of electrolyte and water and the renal contribution to acid-base balance are also of serious import. It is therefore apparent that although a generalized aminoaciduria may be of no particular metabolic significance in itself, it is of value to suggest the necessity of further studies to assess the full extent of the renal tubular defect. There is also the important fact that these generalized renal aminoacidurias are often found in association with other inherited abnormalities such as cystine storage disease (cystinosis) (15), galactosemia (16), or diseases affecting mental development, as in Lowe’s syndrome (17).

Manifestations of the Fanconi syndrome may also be observed in adults (18). Although usually these are acquired as a result of concurrent involvement of the kidney by a pathologic process, there is evidence that in some instances the adult manifestation of the syndrome is on an inherited basis. The consequences of the renal tubular phosphate leak are most prominent in these cases. Here the defect is recognized as a form of osteomalacia (the analogue of the renal rickets described in the childhood form of Fanconi disease). It is believed that this was actually the cause of the osteomalacia in the case described by Milkman (19) and of the similar cases of “idiopathic” osteomalacia subsequently described and eponymically designated “Milkman’s syndrome.”
Cystinuria

The aminoacidurias characterized by the excretion of relatively few amino acids are best illustrated by the inherited disease of renal tubular transport usually referred to as cystinuria. In this disease four amino acids—cystine, lysine, arginine, and ornithine—are excreted in large quantities. Indeed, from clearance studies \(^{20, 21}\), which indicate that the clearance of several of the affected amino acids approaches that of inulin, it has been concluded that the renal tubular mechanism involving transport of these four amino acids is virtually inactive. No deleterious metabolic result follows the conspicuous aminoaciduria of cystinuria except the likelihood of the occurrence of cystine calculi and consequent renal damage attendant upon the inability to keep in solution such large quantities of cystine as are present in the urine of the cystinuric patient.

Glycinuria; Hartnup (H) Disease

More specific manifestations of defects in renal tubular transport for amino acids are exemplified by glycinuria \(^{22}\) and the aminoaciduria of Hartnup (H) disease \(^{23}\), although in these diseases the metabolic defect may well be much more generalized. For example, in patients diagnosed as exhibiting H disease, dermal symptoms may be present, consisting of an intermittent, red, scaly, pellagra-like rash appearing after exposure to sunlight, and there may also be attacks of cerebellar ataxia as well as psychiatric changes. However, the renal aminoaciduria is a constant feature, and indeed this is the most reliable diagnostic feature of the disease. The aminoaciduria is not generalized, but its pattern is very characteristic. There is a significantly increased excretion of alanine, asparagine, glutamine, histidine, isoleucine, leucine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine. The excretion of the other naturally occurring amino acids remains normal. It is of interest that in the aminoaciduria of H disease, none of the four amino acids excreted in greatly increased amounts in cystinuria is involved.

Glycinuria has been recognized in 4 female members of three generations of a single family. Although experience with this aminoaciduria is still limited, it would appear to be attributable to a selective renal tubular defect in glycine transport. However, 3 of the glycinuric subjects also had a nephrolithiasis due chiefly to calcium oxalate. The fact that glycine is a metabolic source of endogenous oxalate may indicate
that glycinuria has other metabolic manifestations in addition to that affecting the renal tubular reabsorption of glycine.

It must be evident that a continuing study of the aminoacidurias, made more expeditious by the recent introduction of improved technical methods, will prove increasingly fruitful in the elucidation of disease entities of obscure etiology.

**Summary**

The normal mechanisms whereby the renal tubules handle amino acids are reviewed as a basis for interpretation of the physiologic causes of the renal aminoacidurias. Under normal circumstances, the renal tubules reabsorb in excess of 93% of the amino acids filtered from the plasma. When the filtered load of amino acids is increased, as by intravenous injection of amino acids, there is an increase in both the amounts reabsorbed and those excreted, but the ability of the renal tubule to respond to an increased filtered load of amino acids is so great that a maximum rate of reabsorption has not been found in the human. However, the tubule does exhibit selectivity with respect to the reabsorption of each of the naturally occurring L-amino acids; furthermore, there is a much greater efficiency of reabsorption of the L as compared to the D isomers of the individual amino acids.

The excretion of amino acids is influenced to an important degree by the glomerular filtration rate, as exemplified by studies in pregnant subjects as well as patients with renal disease affecting glomerular filtration.

Several renal aminoacidurias of clinical interest are discussed with special reference to their diagnostic and metabolic significance.

**References**