measure secretory as well as reabsorptive mechanisms. A common reabsorptive process for cystine, lysine, arginine, and ornithine could be obscured in vitro by a secretory mechanism specific for cystine (see *5, 14*).

The report by Scriver and Wilson (*15*) demonstrates more than a single renal reabsorptive mechanism for the imino acids and glycine. Additional experiments are needed to determine whether other substances reabsorbed in the proximal tubule also demonstrate multiple transport systems under specific genetic control.

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Amino Acid Transport: Evidence for Genetic Control of Two Types in Human Kidney

Abstract. *A mutation affecting renal transport of proline, hydroxyproline, and glycerine occurs in man. In the presumed homozygote there is still significant residual transport of these compounds; however, this remaining function is saturated at normal concentrations of substrate in the plasma and is not inhibited by* L*-proline in the expected way. The presumed heterozygote has partial loss of a transport system common to the three substrates, which becomes saturated at high concentrations of substrate and is inhibited by* L*-proline. Two different types of transport systems are proposed: a common system and systems with lower capacity and greater specificity. The two types of transport appear to be controlled by separate genes.*

Absorption of amino acids in the intestine and renal tubule of man and other mammals appears to be accomplished either wholly, or in part, by five transport systems, each of which is common to a particular group of amino acids, classified as follows: (i) dicarboxylic-monoamino (acidic) (*1*); (ii) diamino-monocarboxylic (basic) (*2*) —this group also has a complex relation to the transport of L-cystine, which is not a basic amino acid; (iii) glycine and the "imino acids" proline and hydroxyproline (*3*); (iv) a large group of neutral aliphatic, aromatic, and heterocyclic α-amino acids (*4*); and (v) the β-amino compounds (*5*). A common transport system exhibits certain characteristics, both in vivo and in vitro, which imply a mediated or carrier type of function (*1–3*). Specificity is expressed as preferential affinity for its own group of substrates; members of the substrate group can saturate the system and can competitively inhibit the uptake of the other members. The occurrence of mutant genes causing impairment of transport function in both kidney and intestine, as in cystinuria (*2*) where cystine and the basic amino acids lysine, arginine, and ornithine are affected, and in Hartnup disease (*4*) where the large group of neutral α-amino acids is involved, also implicates genetic control of some of these common transport systems.

An explanation for two intriguing observations in mutant transport phenotypes has long been wanting. First, at normal plasma concentrations of basic amino acids in cystinuric homozygotes and of the neutral amino acids in the Hartnup homozygote, the major portion of tubular transport activity is still retained. Secondly, Robson and Rose (*6*) observed during their investigations of the common transport system for basic amino acids, that intravenous infusions of lysine produced little or no further inhibition of tubular absorption of basic amino acids in some homozygous cystinurics, unlike the brisk inhibition produced by the same procedure in normal subjects. Recent investigation of another "experiment of nature" affecting renal tubular absorption of the imino acids and glycine, has provided an opportunity to interpret these earlier observations.

In the human infant selective impairment of tubular absorption of the imino acids and glycine is a normal occurrence for several weeks after birth (*7*). Occasionally imino-glycinuria persists into childhood (*8*), where it has been considered as another example of a selective, and probably inherited, defect in amino-acid transport. We have recently found an otherwise healthy 42-year-old man who has urinary hyperexcretion of proline, hydroxyproline, and glycine; partial impairment of net tubular absorption of these three compounds was documented in this subject (Table 1). The propositus is an Ashkenazic Jew, whose mother died of hepatic carcinoma in her 68th year. His father exhibits hyperglycinuria without iminoaciduria (*9*). One brother and one sister also have hyperglycinuria with diminished net tubular absorption of this amino acid (Table 1). An additional brother has normal aminoaciduria. The propositus is married to an unrelated woman, who has normal aminoaciduria; all three children of this marriage each have hyperglycinuria without iminoaciduria. The propositus is therefore presumed to be homozygous for a mutation affecting the common transport system for imino acids and glycine; his hyperglycinuric relatives are presumed to be heterozygous for the same mutation; four of them were available for estimation of endogenous renal clearance of amino acids (Table 1).

Renal tubular transport of L-proline was investigated (*9*) in more detail in the homozygous and heterozygous mutant phenotypes. A maximum rate (Tm) for net tubular absorption of L-proline exists in the normal subject (*3*); L-proline is also an inhibitor (presumably competitive) (*3*) of renal transport of hydroxy-L-proline and glycine. When the mutant homozygote was infused with L-proline, he was unable to increase the rate of net tubular transport of this imino acid above the value observed before infusion (Fig. 1A). The heterozygote transported L-proline at the normal rate until the Tm was reached (Fig. 1A); however, the Tm was only about half of the normal value. When the urinary excretion of L-proline is expressed as a function of its plasma concentration (Fig. 1B), the threshold for prolinuria is markedly reduced in the homozygote and less so in the heterozygote. The altered kinetics of transport of L-proline in the presumed heterozygote suggest that the common system that transports proline at concentrations above the normal plasma concentration is modified in its capacity, but not in its affinity, for L-proline in this mutant phenotype.

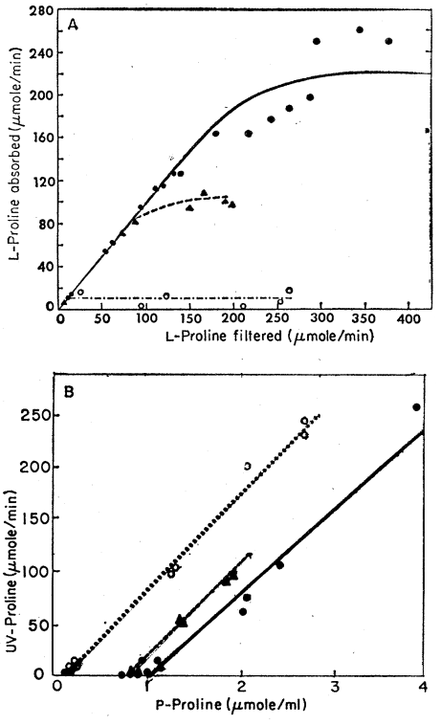

Fig. 1. (A) Tubular absorption of L-proline plotted as a function of the filtered load. Methods of infusion and analysis are described elsewhere (*3, 9*). Normal subjects (●——●); wide range represents interindividual variation. Presumed heterozygote (surface area, 1.1 m²) showing small low Tm but normal uptake below Tm (▲——▲). Presumed homozygote (surface area, 1.70 m²) showing small residual transport activity but no further capacity for L-proline transport (○—•—○). (B) Prolinuria plotted as a function of concentration in venous plasma.

Table 1. Renal clearance and tubular absorption of L-proline, hydroxy-L-proline, and glycine in fasting subjects. Twelve normals, one homozygote (studied twice), and four heterozygotes were studied. Endogenous renal clearance is expressed in milliliters per minute per 1.73 m² (*9*). Tubular absorption is expressed as percentage of filtered load of amino acid (*9*).

Endogenous renal clearance				Tubular absorption		
L-proline	Hydroxy-L-proline*	Glycine		L-proline	Hydroxy-L-proline*	Glycine
			Normals			
0–0.3	0	1.2–8.6		99.8–100	100	93–99
			Homozygote			
15.9,19.6	32,31	29.7,33.6		82,77	65,67	69,63
			Heterozygote			
0–0.3	0	10.8–18.6		99.8–100	100	82–86

* Ion-exchange chromatographic analysis of hydroxyproline in plasma revealed that the concentration of this amino acid did not exceed 0.01 μmole/ml. Accurate assessment of concentration below this level is not possible with this method; calculations of tubular absorption were based on a plasma value assumed to be 0.01 μmole/ml.

The effect of L-proline upon net renal tubular absorption of glycine and hydroxyproline was also measured in mutant and normal phenotypes (Table 2). A substantial increase in the plasma concentration of L-proline considerably inhibits absorption of glycine and hydroxyproline in the normal subject (*3*). However, L-proline caused no additional inhibition of glycine transport in the presumed homozygote, even though the proline concentration was increased more than tenfold. Inhibition of glycine absorption occurred in the heterozygote (Table 2), but only about half the concentration of inhibitor (L-proline) was required to produce inhibition comparable to that which can be obtained in normal subjects. Moreover, when net tubular absorption of glycine had been depressed to 60 percent of its filtered load in the heterozygote, no further inhibition was achieved despite a further twofold increase in the concentration of inhibitor. The amount of glycine transport "lost" in the mutant homozygote is comparable to the amount impaired when L-proline inhibition is maximum in the heterozygote and in normal subjects; that amount is approximately 8 μmole/min per 1.73 m².

The excretion of hydroxyproline increased in all three phenotypes after infusion of L-proline (Table 2). This response in the mutant homozygote suggests that the remaining transport available to hydroxyproline is different from the glycine transport function that cannot be inhibited.

These observations reveal that two types of absorptive mechanisms operate to transport the imino acids and glycine from the glomerular filtrate into the tubular cells. One type (A system, Fig. 2) has group specificity, is common to all three substrates, and has "high" capacity. Since either imino acid can inhibit the transport of the other and of glycine (*3*) by this system, it appears that it has a rather low order of affinity for its substrates. Studies of the normal human subject,

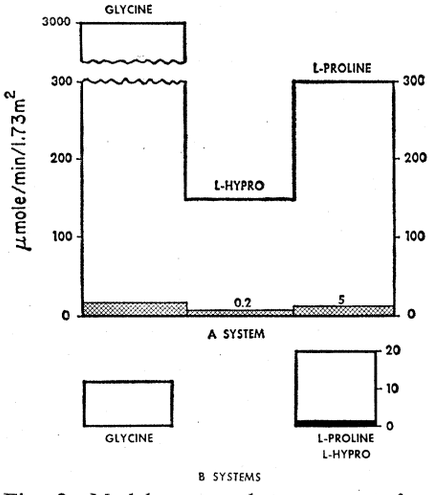

Fig. 2. Model proposed to account for observations on transport of imino acids and glycine in normal and mutant phenotypes. The capacities of the A system are derived from Tm studies in man for the two imino acids (*3*), and in the dog for glycine (*16*); the A system is "common" to the three substrates and can be inhibited competitively (*3*). Transport by this system is missing in the homozygote and partially absent in the heterozygote. The A system is used to a small extent at normal endogenous plasma concentrations (hatched portion of block), accounting for hyperaminoaciduria in mutant phenotype. Two B systems are proposed, one for glycine and one for the imino acids (solid portion of imino acid system represents hydroxyproline transport). These systems are saturated at normal endogenous plasma concentrations of substrate; their capacity is calculated from data obtained in the presumed homozygote.

Table 2. Effect of infusion of L-proline on absorption and excretion of glycine and hydroxyproline, respectively. Three normals, one homozygote, and one heterozygote were studied. The rate of hydroxyproline excretion rather than its absorption rate is given because of the difficulties in accurately measuring the filtered load of hydroxyproline. Determinations were made before infusion of L-proline and at Tm for proline.

Glycine absorption (% filtered load)		Hydroxyproline excretion* (μmole/min per 1.73 m²)	
Before infusion	At Tm proline	Before infusion	At Tm proline
	Normal		
93–99	58–61*	0	0.5–1.5
	Homozygote		
63	60	0.3	1.5
	Heterozygote		
83	60*	0	1.2

* The filtered load of L-proline required to achieve this amount of inhibition is greater than 225 μmole/min per 1.73 m² in normal subjects; the heterozygote subject required only 150 μmole/min per 1.73 m².

and of the rat kidney cortex in vitro (*3*) indicate that L-proline has the highest affinity and glycine the least affinity for the common system.

It is this system which appears to be totally absent in the mutant homozygous phenotype and partially deleted in the heterozygote. The latter phenotype presumably exhibits hyperglycinuria alone because the imino acids have sufficient and preferential affinity for the reduced amount of the common transport system, and thus they are still completely transported by it at normal plasma concentrations.

A second type of transport mechanism can be discerned (type B) in the mutant phenotype where the A system is nonfunctional. The remaining transport activity has a small capacity by comparison with that available on the A system; the proline B system is in fact saturated at normal plasma concentrations of substrate. Glycine is transported on a B system, which is presumably also saturated at low concentrations. This system has considerable affinity and specificity for glycine uptake since it cannot be inhibited by L-proline. Hydroxyproline appears to be transported differently from glycine on a B system; its transport is more readily inhibited than that of glycine by L-proline, indicating that the order of affinity of these two compounds for uptake by B system is the reverse of that for the A system (*3*). Hydroxyproline behaves as if transported on a second B system, distinct from glycine, and which it may share with L-proline (Fig. 2).

The proposed model explains the observations on transport of imino acids and glycine. A similar type of organization may also exist in relation to other "common" transport systems. The evidence, presented by Rosenberg and Segal (*10*), for more than one type of transport for a basic amino acid supports the extension of the hypothesis. If the proposal is valid, then separate genes would appear to control A and B systems. Mutation at an A-system gene could occur without any effect on the B system. Conversely, mutation could occur in a B-system gene without effect on the related A system. Perhaps those diseases claimed to manifest selective impairment of transport of methionine (*11*) and tryptophan (*12*) will prove to be examples of the latter type of mutation (*13*). Proposals for the occurrence of more than one type of transport mechanism available to a single amino acid have also been advanced for transport of certain α-amino acids in gram-negative bacteria (*14*), and ascites tumor cells display more than one mediation for uptake of β-alanine (*15*).

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Ecological Dosimetry: Radiation Levels Influenced by Plant Growth

Abstract. *The feasibility of using lithium-7-fluoride thermoluminescent dosimeters under field conditions for natural radiation at levels of 5 milliroentgens is demonstrated. Radiation dosages in tree trunks increased threefold from winter to spring and summer. This increase is attributed to the gamma radiation field resulting from relatively high levels of potassium-40 and other radionuclides present in the foliage and branches during the growing season.*

The radiation environment of a tree injected with radionuclides varies with season (*1*). In principle this seasonal variation should exist for all deciduous trees from the redistribution of radioactivity in the soil. Sources include potassium-40, members of the uranium (radium) and thorium series, and fallout. The hitherto lack of sufficiently sensitive dosimeters which could be left in place for extended periods of time has limited potential analyses of variations in the environmental radiation.

Thermoluminescent radiation dosim-