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# DISTURBANCES OF AMINO ACID METABOLISM*

*The Fifth Harlow Brooks Lecture*

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THE subject of abnormalities of amino acid metabolism is a broad one, including as it does a variety of conditions in which abnormal proteins are formed or in which normal proteins are inadequately formed or destroyed. The present discussion will be confined to a limited area—a group of conditions in which abnormalities in the metabolism of particular amino acids are identifiable by abnormal plasma levels or by abnormal excretion patterns of amino acids, or their derivatives, in the urine. Some of these conditions fall into the group of inborn errors of metabolism and others are acquired.

Our knowledge of this group of disorders goes back to 1810 when Wollaston[1] described and analyzed a cystine calculus in a patient with cystinuria. This was the first amino acid to be identified. For some years

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little further progress was made, but toward the end of the last century knowledge about other amino acids developed rapidly, as chemical methods for the identification of particular amino acids became available and many new anomalies of metabolism came to light. The application of these chemical procedures to the blood as well as to the urine enabled Dent[2] to classify the aminoacidurias into two groups—*the renal aminoacidurias,* in which the body metabolism was normal with the exception of the kidneys, where defective tubular reabsorption of certain amino acids led to increased renal excretion, and the *overflow aminoacidurias,* in which an excess of one or more amino acids in the urine could be attributed to an increased concentration in the blood. We should like to extend Dent's classification to include two more groups. These may be designated as the *underflow aminoacidurias,* in which a diminished blood concentration results in a diminished urinary excretion, and a group that may be described as *masked aminoaciduria,* in which there may be little or no abnormality of amino acid excretion, but in which a metabolic fault of amino acid metabolism leads to the excretion of some product derived from an amino acid. A further subdivision of these groups may be made depending upon whether the condition is congenital or acquired, whether it affects all amino acids or only specific ones and, in the case of the renal group, whether it is associated with other defects of tubular absorption. Certain entities are mixed—renal and prerenal factors both playing a part.

Some confusion in the literature has resulted from the lack of agreement in defining hyperaminoaciduria. Several standards of reference have been used: (a) the total daily excretion, (b) the excretion per kilogram of body weight, (c) the ratio of alpha-amino nitrogen to total nitrogen in the urine ("amino acid index") and (d) the ratio of alpha-amino nitrogen to creatinine in the urine ("amino acid-creatinine index"). Each of these criteria is open to some objection. Age and diet affect amino acid excretion[3]. From the limited data available obtained with modern column chromatographic methods, it appears that on commonly employed European and American diets there is, after the disappearance of the neonatal hyperaminoaciduria, a gradual increase in total amino acid output; standards for each age are, however, not adequately established. The nature of the dietary protein exerts little effect on the total amino acid output, far less so than on the urea or total N output. The amino acid index

TABLE I—CLASSIFICATION OF AMINOACIDURIAS

| | |
|---|---|
| I. THE RENAL HYPERAMINOACIDURIAS | |
| *A. Generalized* | *Associated tubular absorptive defects* |
| Fanconi syndrome (De Toni-Fanconi-Debré) | glucose, P |
| Cystinosis (Lignac-Abderhalden) | glucose, P |
| Oculo-cerebral dystrophy (Lowe) | glucose, P |
| Hepato-lenticular degeneration (Wilson's disease) | glucose, P, uric acid? |
| Luder-Sheldon syndrome | glucose |
| Galactosemia | P? |
| Poisons (lead, cadmium, uranium, lysol, oxalic acid, maleic acid) | ?glucose ?P |
| Rickets (vitamin D deficiency) | P |
| Rickets (resistant—some cases) | P |
| Scurvy | |
| Congenital tubular renal acidosis (Lightwood syndrome) | |
| Renal disease (organic)—some cases | |
| Hartnup syndrome | |
| Premature and newborn infants | |
| *B. Specific* | *Amino acid chiefly affected* |
| Cystinuria | cystine, lysine, ornithine, arginine |
| Hydroxyamino aciduria (cadmium poisoning) | threonine, serine |
| "T" spot pattern | β-amino isobutyric acid |
| Renal glycinuria | glycine |
| Pregnancy | histidine |
| II. THE OVERFLOW (prerenal or metabolic) HYPERAMINOACIDURIAS | |
| *A. Generalized* | |
| Premature and newborn infants | |
| Liver disease | |
| Hepatolenticular degeneration (late) | |
| Muscular dystrophy | |
| Burns | |
| Surgery | |
| Irradiation | |
| *B. Specific* | *Amino acid chiefly affected* |
| Phenylketonuria | Phenylalanine |
| Maple syrup urine disease | Methionine, leucine, isoleucine, valine |
| Cystathioninuria | Methionine |
| Arginosuccinuria | Arginine |
| Sporadic cretinism | Tyrosine |
| Childs-Cooke syndrome | Glycine |
| Hartnup disease (?) | Tryptophan |
| Marfan's syndrome (?) | Hydroxyproline |
| III. UNDERFLOW AMINOACIDURIAS (hypoaminoaciduria) | |
| *A. Generalized* | |
| Kwashiorkor | |
| *B. Specific* | |
| Maple sugar urine disease | |
| Experimental amino acid deficiencies | |
| IV. MASKED AMINOACIDURIAS (abnormal excretion of products derived from amino acids) | *Amino acid chiefly affected* |
| Alkaptonuria | Tyrosine |
| Tyrosyluria | Tyrosine |
| Pyridoxine deficiency | Tryptophan |
| Oxalosis | Glycine |

$\left(\frac{\alpha \text{ amino N}}{\text{total N}} \times 100\right)$ is open to the objection that it readily reflects changes in total N excretion caused by variations in nitrogen intake. In our opinion the ratio of α-amino nitrogen to creatinine, first used by Fowler[3] and Cheung[4], is the most satisfactory criterion available, creatinine excretion being less susceptible to variations in dietary nitrogen than is nitrogen excretion as a whole. Hyperaminoaciduria may be said to exist: 1) if the output of alpha amino nitrogen exceeds 4 mg. per kilo per day; 2) if the alpha amino nitrogen comprises more than 2 per cent of the urinary nitrogen or 3) if the alpha amino nitrogen/creatinine ratio exceeds 0.6.

A classification of the various aminoacidurias is shown in the accompanying table (Table I).

## I. The Renal Hyperaminoacidurias

The pattern of amino acid excretion found in the various renal hyperaminoacidurias varies to some extent from one condition to another and from one individual to another. In general, however, all the amino acids tend to be increased.

### A. Generalized Renal Hyperaminoaciduria

*The Fanconi syndrome*, to which several other investigators' names are attached[5], is the best known example of this group[6], and the excretion of amino acids in this condition is particularly marked, often more than 10 times the normal figure. A peculiar morphological defect of the proximal tubule has been described by Clay, Darmady and Hawkins[7]—a constriction known as the "swan neck" deformity (Figure 1). As is the case with a number of other renal aminoacidurias, the tubular reabsorptive defect involves glucose and phosphorus as well as amino acids, and resistant rickets is a prominent clinical manifestation. The disease is in most instances congenital, but acquired cases have been described.

Very similar to the Fanconi syndrome, and at one time confused with it[8], is *cystinosis*, a condition first observed by Lignac[9] and by Abderhalden[10]. It is a generalized disease in which cystine crystals are found deposited throughout the body, being most readily detected during life in the cornea by a slit-lamp examination. The explanation of this abnormal deposition is not known. The generalized aminoaciduria

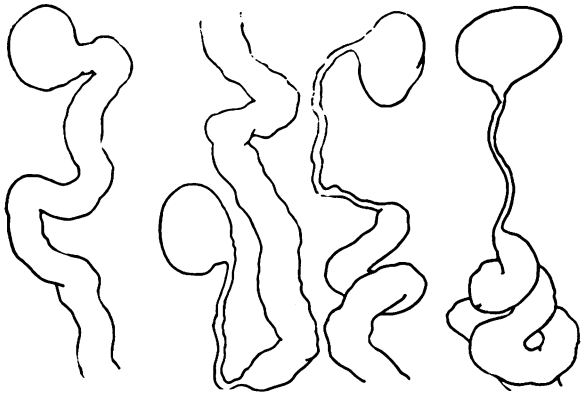

Fig. 1—Outline drawing of the first part of three nephrons, showing that in the Fanconi syndrome the glomeruli are attached by a narrow elongated neck to the proximal convoluted tubule. A normal nephron is seen on the left. (From Clay, Darmady and Hawkins[7].)

is attributed to the deposition of cystine crystals in the tubular epithelium. Cystine is not prominent in the amino acid excretion pattern—in sharp contrast to cystinuria. Bone symptoms are usually conspicuous.

*The Lowe syndrome*[11] (oculo-cerebral dystrophy) is a generalized disorder associated with a renal aminoaciduria. The clinical picture differs very strikingly from the previously mentioned conditions. Mental defect, which is mild or absent in the previously mentioned disorders, is extreme in the Lowe syndrome. Congenital glaucoma is commonly present and at times there are other ocular malformations.

*Wilson's disease* (hepatolenticular degeneration) is now known to be a disorder of copper metabolism in which the synthesis of a copper-containing protein—ceruloplasmin—is defective[12]. Abnormal deposition of unutilized copper occurs in the tissues and its deposition in the renal tubule is regarded as responsible for the defects of tubular reabsorption. Early in the disease a purely renal aminoaciduria is present but in later stages, with hepatic involvement, hyperaminoacidemia develops and accounts for part of the increased urinary amino acid output[13, 14].

*Luder and Sheldon*[15] observed a tubular reabsorptive defect involving glucose and amino acids alone, phosphorus reabsorption being normal. This occurred in three generations, and was virtually asymptomatic.

*Galactosemia*[16-18]: In this congenital disorder the renal tubule appears to be damaged by galactose or by the abnormal accumulation of a me-

tabolite which may be galactose-1-phosphate. The hyperaminoaciduria is readily abolished by a galactose-free diet.

A variety of *tubular poisons* may lead to renal hyperaminoaciduria, including lead[19], mercury[20], cadmium[20], copper[20], uranium[21], lysol[22], oxalic acid[23] and maleic acid[23]. The severity of the disturbance varies, as might be expected. Glucose and phosphate reabsorption, too, are likely to be affected.

*Rickets and scurvy:* A moderate degree of generalized aminoaciduria was described in ordinary rickets by Jonxis and Huisman[24, 25]. In resistant rickets this has also been reported[25], though this appears not to be a constant finding[26]. In scurvy[27] a generalized aminoaciduria has also been described. This is quite apart from the abnormal excretion of tyrosine metabolites observed in that condition, which are discussed later.

*Congenital renal tubular acidosis* (Lightwood syndrome): The presence of a generalized renal aminoaciduria in this condition has been pointed out by Harrison[26], who observed it in three children. Correction of the acidosis with alkali results in a return of the amino acid excretion to normal.

*Renal disease* (organic): Inconstant findings are reported in cases of acute and chronic nephritis[28, 29]. In nephrotic children, however, Woolf and Giles[30] reported definite abnormalities. Early in the disease a generalized pattern was observed, whereas in several late cases a somewhat different pattern, in which ethanolamine, $\beta$-amino-isobutyric acid and taurine were prominent, was described. This they associate with a degenerative process. Kretschmer[31] regards aminoaciduria as a bad prognostic sign in nephrosis.

*Hartnup disease:* This familial disorder associated with a pellagra-like rash, cerebellar ataxia, mental defect and a generalized aminoaciduria was described by Baron, Dent and their co-workers[32]. In addition they reported the presence of abnormal tryptophan metabolites, which suggested a specific defect in the metabolism of this amino acid.

*Premature and newborn infants:* A number of observers have reported on hyperaminoaciduria of the newborn[3, 33, 34]. The condition occurs more strikingly in premature infants. Although a hyperaminoacidemia is present in the postnatal period it does not appear adequate to account for the extent of the urinary excretion, which must therefore be classified as a combination of renal and prerenal disturbance.

B. THE SPECIFIC RENAL HYPERAMINOACIDURIAS

*Cystinuria* (cystine-lysinuria): For long regarded as a disorder of metabolism, it remained for Dent and his co-workers[35, 36] to show that cystinuria was essentially a renal disorder, the blood cystine level not being elevated and indeed often abnormally low. Three other amino acids are excreted in excess—lysine, ornithine and arginine. The excretion of lysine is comparable in magnitude to that of cystine and in some cases exceeds it. Only the cystine, however, gives rise to difficulty, because of its low solubility and the resulting tendency to calculus formation. The excretion of ornithine and arginine is increased to a lesser extent and in some instances only normal quantities are excreted. There is some evidence that mild types of the disease exist, perhaps in heterozygotic individuals.

*Hydroxyamino aciduria:* Clarkson and Kench[20] described a group of subjects suffering from cadmium poisoning who, in addition to a generalized aminoaciduria, excreted exceptionally large amounts of threonine and serine. This was attributed to a specific reabsorptive defect of the two hydroxyacids.

*"T" spot excretion pattern:* The tendency in certain families to exhibit a pattern in which "T" spot, subsequently identified as β-aminoisobutyric acid, was excreted in excess, was described by Crumpler and his co-workers[37]. It is unassociated with symptoms.

*Glycinuria:* A specific familial entity associated with increased excretion of glycine was described by de Vries and associates[38] in patients with nephrolithiasis. The glycinuria was apparently of renal origin.

*Pregnancy:* Several amino acids are found in increased concentrations in the urine in pregnancy[39, 40], but the most striking change occurs in the case of histidine. The aminoaciduria is of renal origin and is explained in part on the basis of increased glomerular filtration rate, in part as a specific tubular reabsorption defect.

## II. THE OVERFLOW (PRERENAL) HYPERAMINOACIDURIAS

A. GENERAL HYPERAMINOACIDURIA associated with hyperaminoacidemia occurs in a variety of conditions associated with tissue damage[41-44]. It is found to a greater extent in liver disease[45-47] than in other situations but has been described in the presence of muscular degeneration, severe burns, surgical trauma and radiation injury.

As explained above, some increase in plasma amino nitrogen levels

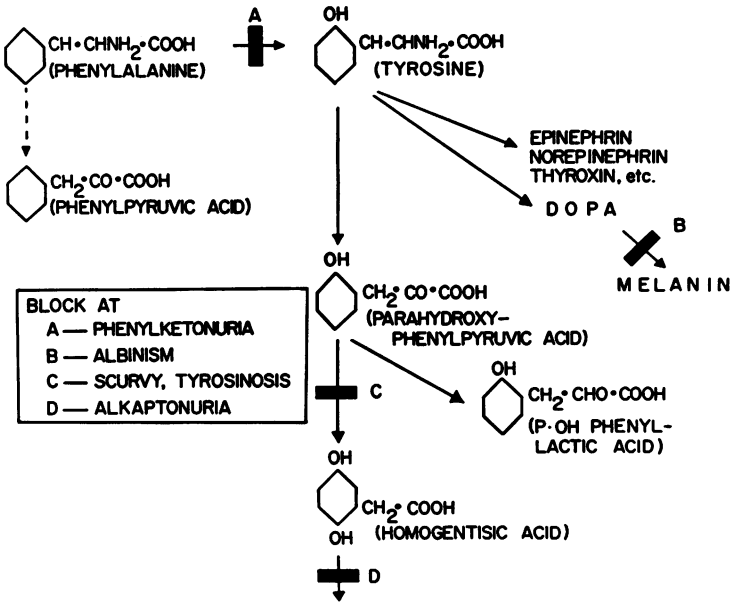


Fig. 2

has been described in the newborn, although not enough to account for the marked and prolonged neonatal hyperaminoaciduria.

B. THE SPECIFIC PRERENAL HYPERAMINOACIDURIAS

Of the six or more entities in this group, all have been associated with mental deficiency, usually of marked degree. The first member of this group to be described and the best known is *phenylketonuria.* In this condition the basic defect is in one component of the enzyme system concerned in the hydroxylation of phenylalanine to form tyrosine[48, 49]. As a result of this defect phenylalanine accumulates in the blood and spinal fluid in large quantity. The plasma level may reach 60 mg. per cent (normal 1 to 1.5 mg.) and the spinal fluid level may contain as much as 8 mg. per cent. Levels of tyrosine are often subnormal. The immediate cause of the brain damage in these patients is not clearly established. It may be due to phenylalanine itself or to abnormal metabolic products which are formed as a result of the metabolic block. Unutilized phenylalanine is in part excreted as such, in part

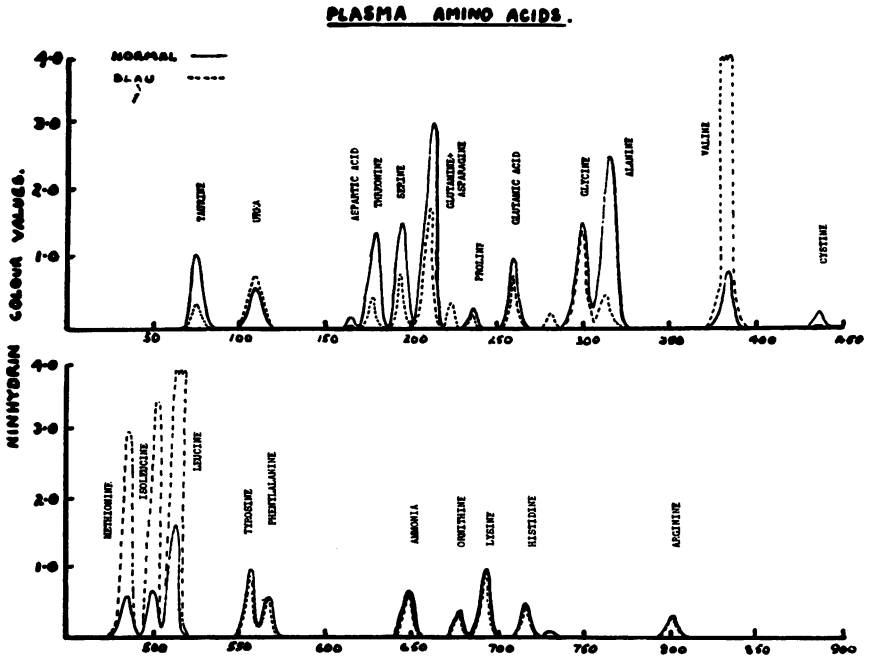


Fig. 3—Plasma amino acids in maple syrup urine disease. The solid line represents normal value, the dotted line being that of a patient. From Westall et al.[57, 59] Reproduced by permission of the publisher and authors.

transaminated to form the keto derivative, phenylpyruvic acid (Figure 2). From the latter a number of other metabolic products are derived, including phenyllactic and phenylacetic acid, the latter giving a characteristic odor to the urine. A secondary derangement of tryptophan metabolism occurs with decreased formation of 5-hydroxy derivatives including serotonin[50]. Some of the clinical abnormalities—such as the blond hair—are apparently due to a deficit of tyrosine[51], since it has been found[52] that the hair pigment can be restored by a tyrosine supplement.

The disease has attracted great interest since it has been found that the abnormal chemical findings may be reversed by the administration of a phenylalanine-poor diet[53-55]. Improvement in cerebral function occurs only if this is done very early in life. From present information it would appear that if the corrective diet is instituted during the early weeks of life—either in the first or second month—virtually normal

mentality may be expected. A considerable benefit is obtained if the diet is corrected during the latter part of the first year, but after the age of two years the benefit is negligible. It is not known how long the corrective diet must be given. There is some reason to think that it does not need to be life-long.

*Maple syrup urine disease:* This condition was described by Menkes and his associates in 1954[56], the clinical features being an early onset toward the end of the first week of life, with spasticity, loss of the Moro reflex and rapid cerebral deterioration leading to death in a matter of months, the urine having a peculiar odor resembling that of maple syrup. In 1957 Westall, Dancis and Miller[57, 58] studied the urine and blood of a moribund patient and observed a striking abnormality of the amino acid pattern. The branched chain amino acids—leucine, isoleucine and valine—as well as methionine, were found markedly elevated, whereas cystine and several other amino acids were abnormally low (Figure 3). It was apparent that a specific disturbance of amino acid metabolism was present. Subsequent observations in three laboratories[59-61] have thrown considerable light on the nature of the metabolic block. It appears that in this disease the transamination of methionine and of the branched chain amino acids occurs normally with the formation of the corresponding keto acids, but that further degradation is blocked with the accumulation of the 4 keto acids as well as the 4 amino acids in the blood. Some abnormal metabolites—hydroxy-derivatives of these amino acids—have been identified. There is also evidence of what appears to be a secondary disturbance of tryptophan metabolism. Therapeutic studies now in progress with low intakes of the 4 elevated amino acids have given some encouraging results, but it is not possible to make a definite statement about their value at the present time. The explanation of the low values of certain other amino acids remains to be found.

*Cystathioninuria:* This metabolic anomaly was described by Harris[62] in an elderly female defective patient. During life this patient excreted enormous amounts of cystathionine and large quantities were found postmortem in the liver and kidney. Two male relatives were found to excrete moderate excesses of cystathionine. It is postulated that a metabolic block occurs in the conversion of methionine to cysteine (Fig. 4).

*Arginosuccinuria:* In 1957 Allan and associates[63] described two mentally deficient children in a family who excreted large amounts of

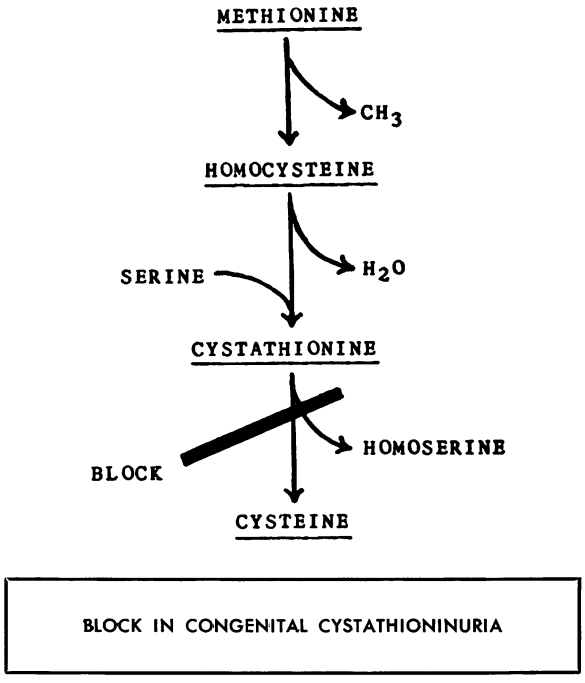


Fig. 4

an unidentified ninhydrin-reacting spot. This substance was later identified by Westall[64] and was found to be L-arginosuccinic acid, an intermediate in the urea cycle. It was found to occur in the cerebrospinal fluid in even larger amounts than in the plasma. The exact nature of the metabolic block is conjectural (Figure 5).

*Goitrous cretinism:* In certain cases of goitrous cretinism[65] mono- and diiodotyrosines are excreted in the urine. The further synthesis of effective thyroid hormones is apparently blocked.

*Childs-Cooke syndrome:* Childs and Cooke[66] recently described a mentally defective child of 18 months who also suffered from episodes of ketosis and neutropenia in which overflow glycinuria was present, the glycine excretion being increased 5 to 19 fold. A disturbance of the interconversion of glycine and serine was postulated.

*Hartnup syndrome:* This[32] has already been mentioned under the renal aminoacidurias and there is no question that the generalized aminoaciduria found in this condition is of renal origin. Some evidence has, however, been obtained by Dent[62] that points to a specific abnormality

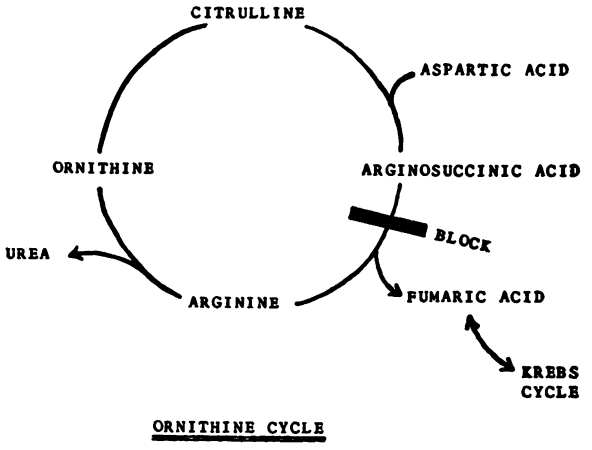


Fig. 5—Postulated metabolic block in arginosuccinuria.

of tryptophan metabolism, namely the excretion of certain tryptophan derivatives–indolacetic acid and indolacetylglutamine (Figure 6). The difficulties of measuring tryptophan accurately in the blood leave doubt as to whether the tryptophan in the blood is actually elevated and whether this can be considered a true overflow aminoaciduria.

*Marfan's syndrome:* A recent report by Sjoerdsma and co-workers[66a] describes the excretion of abnormally high amounts of hydroxyproline in the Marfan syndrome. It is not yet established that this is a metabolic rather than a renal aminoaciduria, although the former seems a more likely possibility.

## III. The "Underflow" Aminoacidurias (Hypoaminoacidemia)

In our studies of the plasma amino acid pattern of kwashiorkor patients from several different countries[67, 68], exceptionally low levels of nearly all amino acids have been encountered; in the more severe forms of the disease the total free amino acid was often less than one third and sometimes as low as one tenth of the normal figure. The reduction in amino acid concentration was not altogether uniform, a consistent finding being that tyrosine suffered more than phenylalanine, suggesting some impairment of the activity of the phenylalanine hydroxylating enzyme. There is also a tendency for the essential amino acids to be depressed more than the unessential ones (Figure 7).

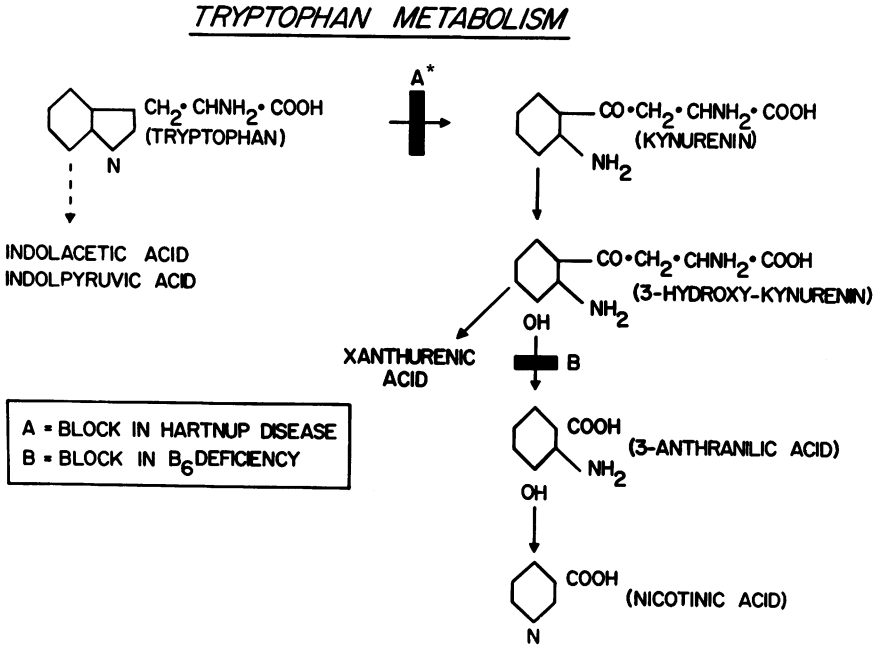


Fig. 6—*Point A on the diagram indicates possible location of the metabolic block in Hartnup disease; the exact location of the block is, however, not as yet identified.

*Specific hypoaminoacidemias* affecting a single amino acid have been observed under experimental conditions in which a particular amino acid has been temporarily omitted from the diet[70]. Reduction in plasma concentration and of the urinary output of the deficient amino acid has been observed under these circumstances.

The specific case of maple syrup urine disease has been mentioned above. In this condition four amino acids were found markedly elevated in the blood and urine while four other amino acids were found to be abnormally low. The explanation of this extraordinary metabolic derangement is not yet clear. The low level of cystine in the presence of an abundance of methionine suggests some interference with the conversion of the latter into the former.

## IV. Conditions Associated with Abnormal Excretion of Amino Acid Derivatives ("Masked Aminoaciduria")

*Alkaptonuria*[71, 72], the first of this group to be discovered, is caused by deficiency of an hepatic enzyme which causes a metabolic block in

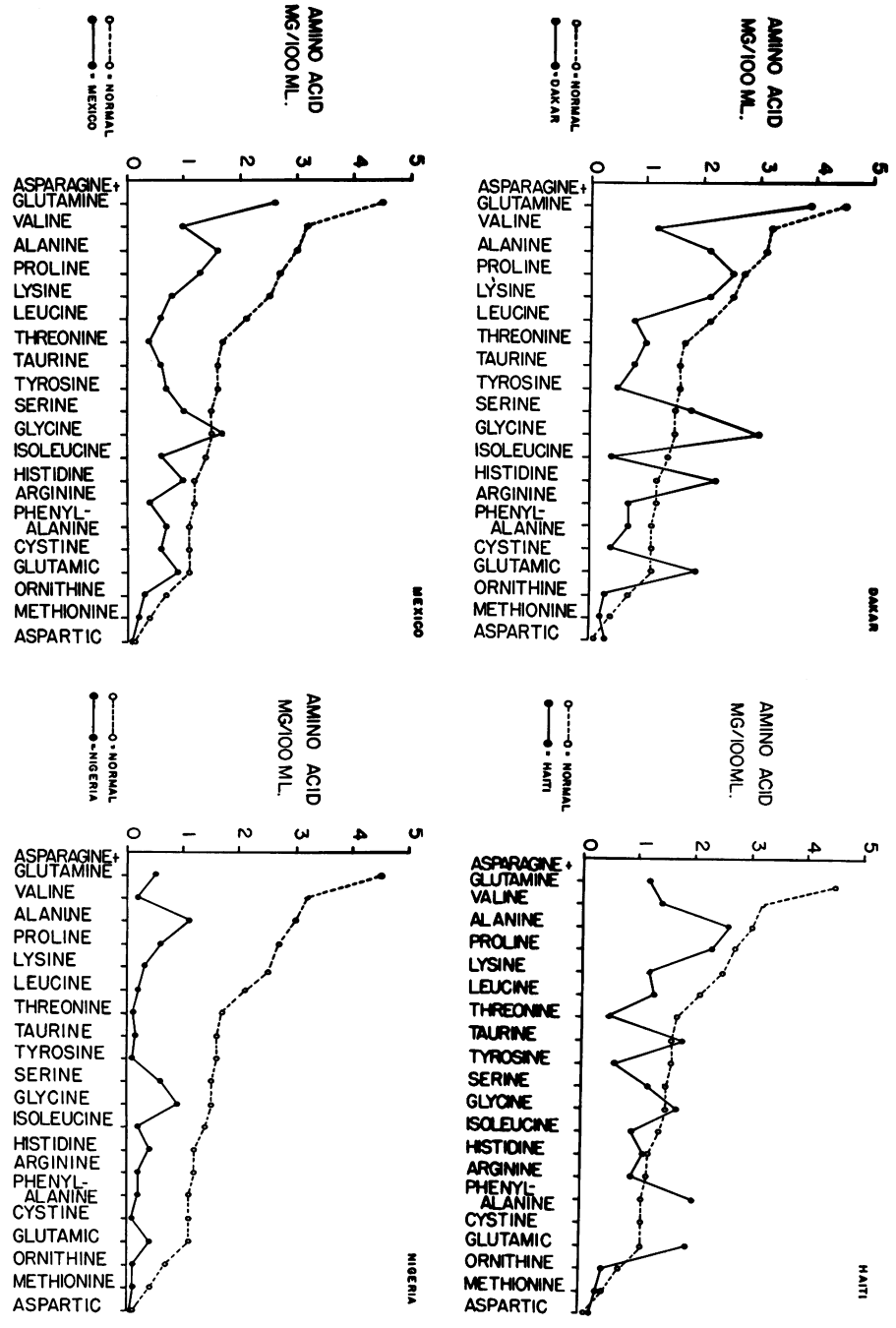


Fig. 7—Plasma amino acids in kwashiorkor.

The graphs are based on average figures obtained from severe cases of kwashiorkor on admission to hospital before any treatment was given (3 cases from Haiti, 4 from Nigeria, 4 from Mexico City and 3 from Dakar). The essential amino acids are depressed to a greater extent than the unessential ones.

the oxidative degradation of tyrosine (Figure 2). As a result of this, homogentisic acid accumulates in the body and is excreted in the urine. The urine darkens on exposure to the air, and early in life this is the only clinical abnormality. In adult life, usually in the third or fourth decades, ochronosis gradually develops with deposition of pigment in the cartilage, skin, sclerae, synovial tissues and fibrous tissues. The deposition of pigment in the joints is often associated with chronic arthritis. The pigment in ochronosis is thought to be a polymer of homogentisic acid or of some closely related product.

*Tyrosyluria:* This term has been applied to the excretion in the urine in considerable amount of two compounds derived from the degradation of tyrosine which are not ordinarily identifiable in urine—parahydroxyphenylpyruvic acid and parahydroxyphenyllactic acid. Their position in the metabolic pathway is shown in Figure 2. Their excretion is commonly associated with an increased output of tyrosine itself. The condition is readily detected with the Millon reagent, which reacts with all these compounds.

This metabolic defect was first described in an asymptomatic adult by Medes[73], who applied the term tyrosinosis to it. Some years later Levine, Gordon and Marples[74] observed the same defect in premature infants fed diets rich in protein, and noted that it was readily abolished by the administration of vitamin C. Subsequent observations[75, 82] have shown that this defect is characteristic of frank scurvy and may indeed be the most sensitive index of vitamin C deficiency. Norton and associates[76] noted high tyrosine as well as phenylalanine levels in the urine of premature infants prior to supplementation with vitamin C.

The relation of tyrosinosis to vitamin C deficiency remained obscure until recently, when patients with this condition were investigated by Felix et al.[83] and by Sakai and Kitagawa[77]. They found that the administration of vitamin C was without effect on the excretion of tyrosyl compounds, suggesting that tyrosinosis is a manifestation of vitamin C resistance.

*Pyridoxine deficiency*[78]. Analogous to tyrosyluria, in which lack or nonavailability of vitamin C causes a metabolic block in the degradation of tyrosine, are states of pyridoxine deficiency or pyridoxine resistance in which the lack or nonavailability of vitamin $B_6$ results in a block in the metabolic degradation of tryptophan (Figure 6). This results in the accumulation and increased output in the urine of several

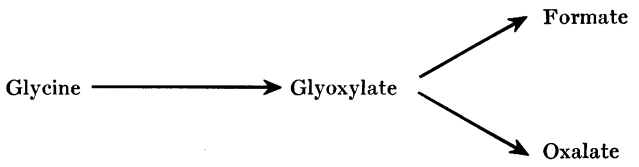


Fig. 8

intermediates in the pathway from tryptophan to niacin, notably: kynurenine, kynurenic acid, their 3-hydroxy derivatives and xanthurenic acid. Administration of $B_6$ in adequate amounts reduces the excretion of these metabolites although they are still detectable in normal urine by refined methods.

It is, of course, well known that pyridoxine plays an important role in the metabolism of amino acids other than tryptophan and indeed in other pathways of tryptophan metabolism, but this particular block caused by pyridoxine deficiency is the most readily detectable.

*Oxalosis*[79, 80]. This is a metabolic disorder in which calcium oxalate crystals are deposited in tissues throughout the body, those in the kidney leading ultimately to renal failure. The oxalate is endogenous in origin, being derived from glycine, as shown in Figure 8. It is not altogether clear why this reaction proceeds with such vigor, but it is supposed that the competitive pathway resulting in the formation of formate is in some way blocked.

Little can be accomplished therapeutically by limiting oxalate-rich foods (rhubarb, spinach and kale) since a negligible fraction of the oxalate is exogenous. Archer and his co-workers[81] have, however, shown that the administration of sodium benzoate to trap glycine with the formation of hippuric acid causes a striking reduction in oxalate excretion.

## Summary

The anomalies of amino acid excretion—renal and prerenal (metabolic)—constitute an important group of disorders which are being discovered and recognized with increasing frequency as technical methods for their identification become available.

The newer procedures of column chromatography which make it possible to measure deficits as well as excesses of particular amino acids

in the blood and urine carry the promise of discovering and perhaps correcting anomalies that have not been revealed by the cruder paper techniques.

A number of specific patterns of abnormal amino acid metabolism are known which are caused by enzyme blocks which may be permanent or temporary. Their identification has in some instances opened the way to dietary therapy, the material proximal to the block being withheld to avoid accumulation of toxic products, and the material distal to the block being supplied as such. A particularly promising field for the identification and correction of such disorders is that of mental deficiency.

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