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Chromatographic Studies of Urinary Amino Acids

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I. CHROMATOGRAPHIC STUDIES OF URINARY AMINO ACIDS

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The fundamental role of the amino acids in the structure and metabolism of the body is well recognized. Dietary protein is absorbed from the gastrointestinal tract almost exclusively as amino acids. The level of the plasma amino acids rises somewhat after a protein meal, but within four hours returns to the postabsorptive level. The amino acids are not stored as such in the tissues to any extent, but are promptly disposed of. They may go to the formation of structural tissue proteins, of plasma proteins and hemoglobin, of enzymes, of some hormones. Or they may go to form essential non-protein nitrogen compounds such as some hormones, choline, creatine, purines, glutathione. They may also lose their amino nitrogen as ammonia, a process which occurs largely in the liver. Most of the ammonia goes to form urea, while the nitrogen-free portion may form glucose or ketone bodies with the subsequent breakdown to carbon dioxide and water and with energy liberation.

Some amino acids are lost into the urine. It is estimated that in the normal person the amount of amino acids in the urine is equivalent to about 1-2% of the amount normally ingested in the diet as protein. Also only about 1-2% of the total urinary nitrogen is made up of amino acid nitrogen.

The ability of the kidney tubule to reabsorb amino acids is a matter of considerable importance, particularly in view of the present practice in clinical medicine of the intravenous administration of protein hydrolysates or other mixtures of amino acids. There, the plasma amino acid levels may reach rather high values. In a study of this problem Wright[1] administered intravenously to dogs each of the ten "essential" amino acids, one at a time. He found that, as the plasma level was raised, increased amounts of the amino acid were found in the urine, but that for 8 of the 10 amino acids, with plasma levels 10-50 times normal, the maximal rate to tubular reabsorption (Tm) had not been reached. That is, no well-defined renal threshold appeared to exist. Two of the 10, arginine and lysine, were not well reabsorbed at elevated plasma levels. Wright found further that there was competition for reabsorption between certain pairs of amino acids (e.g. arginine and lysine, arginine and histidine), but not between other pairs (e.g. arginine and glycine). The results suggest that at least 2 tubular mechanisms exist for the reabsorption of amino acids. This may be a partial explanation for the observation of Kamin and Handler[2] that the intravenous infusion of some one amino acid is accompanied by an increased rate of excretion of other amino acids.

The effect of the intravenous administration of amino acid mixtures on the urinary amino acids in normal human subjects has been studied by Eckhardt et al.[3] They administered 500 ml. of a 10% solution of amino acids (a complete acid hydrolysate of casein supplemented with tryptophane). They found that about 9% of the administered amino acids was lost into the urine within the first 4 hours following infusion, this at a time when the plasma levels were high, and that the excretion returned to normal values after the 4-hour interval. Thus 91% of the administered amino acids were retained and presumably utilized by the body. Where enzymatic protein digests, which contain up to one-third of their amino acids in peptide form, were infused, approximately 45% of the polypeptide alpha amino nitrogen but less than 5% of the free alpha amino nitrogen was lost.

Of the 3 known diseases in humans where the urinary amino acids are grossly elevated - acute yellow atrophy or massive necrosis of the liver, Fanconi syndrome and Wilson's disease - only the first is accompanied by increased plasma

amino acid levels. This suggests that in the last two diseases the defect which is responsible for the gross amino-aciduria is failure of the kidney tubules to reabsorb amino acids.

There is considerable evidence that neither the amount nor nature of protein in the diet has any great effect on the urinary amino acids. Eckhardt et al[3] fed to a normal person for 8-day periods diets adequate in calories and containing 75 or 150 gms. protein per day. The diet with 150 gms. of protein was accompanied by a urinary amino acid excretion only slightly higher than the diet with 75 gms. of protein, and there was no significant decrease during the protein-free period. In studies where the individual "essential" amino acids were measured in persons on diets which varied in the amount and nature of the protein, the excretion of each amino acid was relatively constant.[4,5,6] Further, there was no parallelism between the amino acid pattern in the diet and in the urine.[7] Since the diet appears not to be responsible for the nature and amount of the urinary amino acids it is presumed that the determining factors are the selective removal by the tissues and the degree of reabsorption by the renal tubules.

An exception to the lack of effect of diet on urinary amino acids was seen in the case of the oral administration to a normal subject of an oxidized peptone solution which was markedly low in a number of the essential amino acids.[7] Here the output of amino acids was increased. Presumably in the absence of sufficient amounts of the essential amino acids the tissues were unable to utilize the remaining amino acids and they were excreted.

With this relative independence, then, of urinary amino acids from the nature of the diet, a comparison among individuals of amino acid excretion becomes more feasible than might otherwise have been the case.

Up until the last few years little has been known about the specific amino acids in biological material, largely because specific and practical methods of measurement have not been available. Over the last 6-8 years newer techniques have been introduced. Even yet these have been applied largely to urine, with only a few observations on blood. The two new techniques are: (1) microbiological assay and (2) chromatography.

The microbiological method depends on the failure of a micro-organism to grow in the absence of the amino acid which is to be assayed, and within certain limits the extent of growth is proportional to the amount of the required amino acid present. Almost all of the known alpha amino acids can now be determined microbiologically with the use of different micro-organisms, but the greater part of the published work includes determinations of only some of the known amino acids.

Several types of chromatographic techniques have been introduced for amino acid studies. The simplest and most commonly used of these is partition chromatography on paper. This technique was introduced by Consden et al[8] in 1944, and has found rather wide application in the study of urinary amino acids, especially when used in its 2-dimensional modification. A drawback is that it is not readily adaptible to accurate quantitative measurement, although several techniques for doing so have been proposed.

A second type of chromatography is elution analysis from a starch column. This technique was introduced by Stein and Moore[9] in 1948. It has found applications so far largely in quantitative measurements of the amino acids resulting from the hydrolysis of proteins or polypeptides. After seemingly only preliminary studies on urinary amino acids[10] Moore and Stein[11] have changed from the starch column to a column of sulfonated polystyrene resin. They claim that the latter column gives more satisfactory results for amino acid anaylsis than does starch. In the pres-

ent study both paper and starch column chromatography have been used.

Methods

Twenty four-hour urine collections were obtained, and either used immediately or stored in a refrigerator with thymol for a few days or frozen if kept for longer periods. An aliquot was ultrafiltered by the method of Clegg[12] using collodion membranes, and the ultrafiltrate desalted according to the method described by Consden et al.[13] The desalted ultrafiltrate was concentrated in vacuo, with the bath temperature not over 50° C. The extent of concentration was such that 0.5 cc. contained preferably 0.20-0.25 mg. alpha-amino nitrogen.

Urine hydrolysates were prepared by refluxing an aliquot of the desalted ultrafiltrate for 24 hours with an equal volume of concentrated HCl. The HCl was largely removed by distillation in vacuo, with 2 or 3 additions of water. The residue was taken up in water, neutralized, centrifuged, and the supernatant was desalted to remove especially the large amounts of ammonia formed during hydrolysis. The desalted hydrolysate was concentrated as before.

0.5 ml. of the sample, unhydrolyzed or hydrolyzed, to which proline was often added as a marker, was placed on the starch column, approximately 0.9 X 30 cm., prepared as described by Stein and Moore.[9,14] The greater part of the work was done with propanol: butanol: 0.1N HCl (1:2:1) as the first solvent, with a change to propanol: 0.5N HCl (2:1) part of the way through. A dropcounting automatic fraction collector was used, and 0.5 ml. samples were collected. The chromatogram usually ran until 180-190 ml. were obtained. Each tube or alternate tubes were analyzed for their amino nitrogen content by the ninhydrin colorimetric method of Stein and Moore.[15] Because of the uncertain nature of some of the components, color corrections for the different amino acids were not made.

For most of the paper chromatography studies the 2-dimensional ascending technique was used, using Whatman no. 4 paper, and with phenol-NH_3 as the solvent in the first direction and 2,6 - lutidine for the second solvent, according to the directions of Block.[16] A stainless steel frame, constructed according to the design of Datta et al[17] capable of holding 11 papers, 16 inches square, at a time, was used, and this was placed in a commercially available cabinet which contained the necessary solvent to the depth of a few mm. At least 2 papers, each having had 4 or 5 known amino acids applied, were included in each run. The papers were run in the phenol solvent for about 20 hours, dried overnight in a hood at room temperature, run in the lutidine solvent for about 30 hours, dried overnight, sprayed with 0.2% ninhydrin in 95% ethanol and dried at room temperature. Optimum reading of spots was obtained 4-8 hours after spraying.

Alpha amino nitrogen determinations were done by the manometric ninhydrin method of Van Slyke et al.[18]

Results

Alpha-amino Nitrogen

Table I summarizes the results of 47 alpha-amino nitrogen determinations on the urine of 32 individuals. In the 10 normal adult individuals (4 males, 6 females) the mean value was 128 mg/24 hrs. with a standard deviation of 26, and an actual range of 88-182. These results are in general agreement with those found by other investigators using the same method.[19,20] Hydrolysis of the ultrafiltrate of 5 normals showed increases of 50-90% over the unhydrolyzed values. This degree of increase after hydrolysis is less than that reported by others on non-ultrafiltered specimens.[19,20]

Of 6 patients with liver disease the 4 with post-necrotic cirrhosis all show values above the normal mean but within

Table I

Alpha amino nitrogen excretion

	No. det'n.	No. subj.	Results
Adults			
Normal	16	10	Mean 128±26*mg./24 hrs. Range 88-182 mg./24 hrs. 1.4-3.3 mg./K/24 hrs.
Liver disease			
Post-necrotic cirrhosis	5	4	142,152,153,153, & 161 mg./24 hrs.
Cholangiolitic cirrhosis	3	1	53, 69, & 108 mg./24 hrs.
Alcoholic cirrhosis	1	1	36 mg./24 hrs.
Chronic glomerulo-nephritis	13	10	Range 61-322 mg./24 hrs. (3 of 13 det'n. above normal range)
Wilson's disease	3	1	213, 241, 335 mg./24 hrs.
Progressive muscular dystrophy	2	2	72 & 90 mg./24 hrs.
Children			
Fanconi syndrome C.Y.			176 mg./24 hrs. or 28.2 mg./K/24 hrs. 179 mg./24 hrs. or 29.0 mg./K/24 hrs.
S.Y.			389 mg./24 hrs. or 37.8 mg./K/24 hrs.
Acute yellow atrophy	1	1	243 mg./24 hrs. or 9.7 mg./K/24 hrs.

* Standard deviation

the normal range. No significance can yet be attached to the low or slightly low values in the single cases of cholangiolitic and alcoholic cirrhosis. Ten unclassified cases of glomerulonephritis show a wide range of results, from abnormally low in 2 cases to abnormally elevated in 2 cases. Three determinations on 1 case of Wilson's disease showed considerable variation, but each was above the normal range. Two cases of progressive muscular dystrophy gave values at the low end of the normal range. One of the 2 brothers with Fanconi syndrome was 7 months old and showed on 2 occasions urinary alpha-amino nitrogen values of 176 and 179 mg/24 hrs; the other, 2 years old, had 389 mg. Lacking data on the urinary alpha amino nitrogen on normal children we have attempted to emphasize the markedly elevated excretion of amino acids in these children by expressing their excretion as well as the excretion by normal adults in terms of mg/kg. body weight/24 hours. The last case is that of a 5-year old boy who subsequently died and who showed at autopsy acute yellow atrophy of the liver. He, too, showed markedly elevated amino acid excretion, emphasized when expressed in terms of body weight.

Plasma alpha-amino nitrogen determina-

tions were done on a number of these individuals, including the cases of Fanconi syndrome and Wilson's disease. The only case which showed an abnormal value was in the boy with acute yellow atrophy where the value was 17.0 mg % (upper limit of normal 5.5)

Chromatography

Normals. Starch column and 2-dimensional paper chromatograms were run on 6 normal adults and on 5 patients. The starch column chromatograms showed 10 main peaks, some of which could often be separated into more than 1 component. The peaks have been identified as follows:

(1) Leucine + isoleucine

(2) a. Valine

(3) b. Tyrosine + methionine

(3) Urea

(4) Proline

(5) Alanine + glutamic acid

(6) Threonine + aspartic acid + taurine

(7) a. Serine

b. Glycine + glutamine

(8) Ammonia

(9) a. Lysine

b. Pre - or post - lysine

(10) Histidine

In explanation of peak (9) it should be said that on some chromatograms lysine emerged as a distinct peak. In others there were 2 peaks in the lysine area, and in still others a series of irregular elevations were present. In the 2 latter situations the entire area was classified as lysine plus pre - or post - lysine.

The methods which have been used to identify the peaks are as follows: (1) Comparison with chromatograms of pure amino acids, as established by Moore and Stein.[14] (2) Comparison with a chromatogram of some related amino compounds as determined by Stein and Moore.[10] (3) Addition of single compounds on a column. In this way the locations of taurine and glutamine were established. (4) Addition of a compound to a urine sample which has been run also without the addition. In this way we have established the positions in the chromatogram of leucine, tyrosine, urea, taurine and glutamine. (5) Two-dimensional paper chromatography on the same samples. If certain amino acids could not be detected on paper it seemed justifiable to conclude that they were present, at the most, in very small amounts. (6) Pooling of alternate fractions of a peak, and running on paper with loading. In this way the identities of lysine and histidine were established in the pooled peaks of 3 normal females, and also the absence of an amino acid from the ammonia peak was established.

Paper chromatography has shown that none of the unhydrolyzed samples from normal persons contains glutamic or aspartic acid so that in the unhydrolyzed urine peak (5) becomes alanine, and peak (6) becomes threonine plus taurine. Also, glutamine is destroyed by acid hydrolysis so that peak (7) (b) becomes glycine alone in hydrolysates.

In support of the methods employed in the present study it can be said that they afford a means for measuring quantitatively a pattern of amino acid excretion. The quantitative nature of the results represents a distinct advantage over paper chromatography alone. Certain drawbacks of microbiological techniques are avoided or lessened in the present methods. Among these drawbacks are: (1) inability of micro-organisms sometimes to distinguish between the free and conjugated forms of the amino acid; (2) interference with growth of the micro-organism by certain urinary components such as urea; and (3) inability to detect the presence of an unusual amino compound.

There are limitations in the methods which we have used, or rather to the

degree to which they have been pursued in this study. (1) Complete separation of the known amino acids has not been attained in all cases. The use of different solvents such as those suggested by Stein and Moore[9,14] as well as others still untried would undoubtedly improve the separation. (2) Because of the incomplete resolution and the failure always to return completely to the baseline between peaks, one hesitates to interpret the minor peaks. However some of them have appeared sufficiently frequently that their existence appears to be established although their identity remains obscure. (3) Each peak may contain small amounts of a component in addition to the major one. One must recognize that every spot which shows on paper is likely to represented also on the starch chromatogram. Some urines on paper, especially in the hydrolyzed form, may show as many as 20 spots. It should be emphasized that, at least in our experience, not all samples run with paper chromatography give clear well-resolved chromatograms. Particularly in the unhydrolyzed specimens there may be blurring and tailing, so that interpretation is difficult.

Table II summarizes the quantitative data obtained on the unhydrolyzed fractions (that is, free amino acids) of 6 normal subjects. The results are expressed both as % of total amino nitrogen and as absolute amounts in mg. of amino nitrogen per 24 hours. Owing to the composite nature of some of the peaks it was not possible to express all the results in terms of mg. of the specific amino acid, although this conversion can be made for some of the amino acids.

Table II

Free Urinary Amino Nitrogen in Six Normal Adults

Peak		
Leucine-isoleucine	2.7 (2.2 - 3.4)*	3.3 (3.1 - 3.8)*
Valine	1.0 (0.6 - 1.3)	1.2 (0.9 - 1.4)
Tyrosine-methionine	2.2 (1.5 - 2.8)	2.6 (2.0 - 3.0)
Alanine	5.8 (5.5 - 6.2)	7.4 (5.7 - 8.9)
Threonine-taurine	12.0 (6 - 23)	14.8 (8.1 - 22.0)
Serine	6.9 (5.2 - 9.0)	8.5 (7.5 - 9.6)
Glycine-glutamine	41 (30 - 50)	53.1 (29 - 69)
Lysine - "pre-lysine"	9.4 (6.4 - 11.6)	12.0 (8.4 - 16.0)
Histidine	16.1 (13 - 21)	20.8 (11 - 28)

* Mean and actual range

The results indicate a fair degree of uniformity among the six subjects. The largest spreads are seen in the taurine - threonine peak, in the glycine - glutamine peak and in histidine. In the paper chromatograms one of the normals showed an unusually intense taurine spot, and this is the subject who shows the unusually high taurine - threonine peak. Some taurine could be identified in each of the normal urines. Taurine is a

sufficiently unfamiliar amino compound to deserve special comment. It may be formed in the body from cysteine, being first oxidized to cysteic acid under the influence of an enzyme which is present in liver,[21] and cysteic acid can act as a precursor of taurine[22] which is decarboxylated cysteic acid. It is not known whether or not this is the actual mechanism by which taurine is formed in the body. Taurine has been recognized for years as a component of one type of bile acids, the taurocholic acids, but its presence in the free form in urine (and also in plasma and tissues) has only recently been realized. An unidentified spot was frequently seen on paper chromatograms of urine and it was later identified as taurine. Its significance has not been determined.

Hydrolysis of the protein-free ultrafiltrate caused an increase of 50-90% in alpha-amino nitrogen. Table III presents the results on the 6 normal subjects, with each peak expressed as per cent of the total amino nitrogen. Because of the composite nature of some of the peaks it is not possible to quantitate accurately the specific increases after hydrolysis, but from concomitant studies using paper chromatography it can be said that glutamic and aspartic acids and glycine are largely responsible for the increase of amino acids after hydrolysis. It is presumed that the combined glycine is present as hippuric acid. Nothing is known of the nature of the bound dicarboxylic acids. They may be present in long peptide chains alone or together, which seems unlikely, or their amino groups may be acetylated or bound in some similar fashion. It has been determined that the combined forms of the amino acids are present in the early pre-leucine eluate of the unhydrolyzed specimen. This fraction from a normal urine was collected from 4 large columns, hydrolyzed, and re-chromatographed. It showed large peaks in the glutamic and aspartic acid and glycine areas, very small leucine, valine, and tyrosine-methionine peaks, a larger serine peak, and no amino nitrogen after ammonia. Thus normal urine contains rather large amounts of conjugated glutamic acid, aspartic acid and glycine, a smaller amount of conjugated serine, no con-

Table III

Total Urinary Amino Nitrogen in Six Normal Adults

Peak	% of total amino-N
Leucine - isoleucine	2.1 (1.7 - 2.9)
Valine	1.1 (0.6 - 1.7)
Tyrosine - methionine	1.1 (0.8 - 1.5)
Alanine - glutamic acid	15.6 (14.6 - 16.1)
Threonine - taurine - aspartic acid	14.7 (13 - 19)
Serine	7.0 (5.8 - 9.2)
Glycine	38 (34 - 45)
Lysine - "pre-lysine"	8.5 (3.0 - 8.1)
Histidine	9.5 (6.1 - 12.5)

jugated lysine or histidine, and very small amounts of the conjugated forms of the other amino acids.

Fanconi syndrome.

One of the characteristics of this disease is the presence in the urine of large amounts of amino acids, usually in the presence of a normal plasma amino acid level. The urinary amino acid pattern in this disease has been studied chiefly by Dent[23] who did paper chromatographic studies in 3 cases. His comparisons with normal urines are somewhat unsatisfactory in that he places on paper for both normal and pathological urines either equal volumes of urine or amounts of urine containing equal amounts of nitrogen. This volume represents a much higher content of amino acids in the cases of Fanconi syndrome than it does in normals and one can therefore expect to detect more amino acids in the disease. Dent comments on this difficulty in comparison, but feels that there are certain abnormalities in amino acid distribution in Fanconi syndrome. These will be mentioned later. More recently Anderson et al[24] and Milne et al[25] have each reported one case of Fanconi syndrome, and list the amino acids found by paper chromatography. Differences from normal urines are not obvious from the descriptions.

We have studied by starch column and paper chromatography the urinary amino acids in one case of Fanconi syndrome. The subject was a 7-month old boy (C.Y.), with urinary alpha-amino nitrogen of 29 mg/kg. body weight/24 hours, and a normal plasma alpha amino nitrogen of 3.5 mg %. In all of our studies we place on the starch column or on paper approximately the same amounts of alpha amino nitrogen, so that normal and pathological urines can be quite accurately compared.

Paper chromatograms revealed the absence of taurine, glutamic acid and aspartic acid. The starch chromatogram was unusually well-resolved, presumably because of the small degree of concentration of the urine which was required. In terms of absolute amounts per 24 hours this patient shows an increase over the normal adults range in all peaks except glycine - glutamine, lysine and histidine. The results in terms of % total amino nitrogen are presented in Table IV. The most striking abnormalities are in the relatively high concentrations of the two hydroxy amino acids

Table IV

Free Urinary Amino Nitrogen in Fanconi Syndrome

Peak	% of total amino-N
Leucine - isoleucine	4.3
Valine	2.3
Tyrosine - methionine	3.4
Alanine	9.8
Threonine	16.5
Serine	12.8
Glycine - glutamine	34.7
Lysine	6.3
Histidine	7.7

serine and threonine, which together make up 30% of the total amino nitrogen. Since taurine is absent, the peak which in normals represents threonine and taurine here represents threonine alone. Comparison of Table IV with Table II indicates that the relative concentrations of leucine, valine, tyrosine-methionine and alanine are all higher than in the normal adult, and that, percentagewise, glycine-glutamine is less than in the normal.

The outstanding difference from normal in the hydrolyzed specimen is an increase of only 25% after hydrolysis. In absolute amounts per 24 hours, the content of combined glutamic acid is similar

to that of the normal adult, combined aspartic acid is somewhat less, whereas the amount of glycine in the hydrolysate is less than glycine-glutamine in the unhydrolyzed specimen. This suggests the presence of little, if any, combined glycine.

The significance of these abnormalities is a matter only for speculation, and the consistency of the abnormalities from one case to another remains to be determined. Dent[26] noted the absence of taurine in at least one case of Fanconi syndrome; Anderson[24] lists taurine as a component in his case, Milne[25] does not. Dent[23] is of the opinion that unusually large amounts of the hydroxy amino acids, especially serine, are present in the urine.

The fact that the 2 hydroxy amino acids are excreted in our case in disproportionately large amounts may mean that the mechanism by which these 2 are reabsorbed by the kidney tubules is particularly affected in this disease. Whether or not the continued loss of the "essential" amino acid, threonine, and of the non-essential serine into the urine affects the tissues of the body is not known.

Wilson's disease. (Hepatolenticular degeneration).

One of the features of this disease, too, is excessive excretion of amino acids into the urine. From 2 studies[27,28] using paper chromatography it was concluded that the aminoaciduria was general, that no single amino acid predominated. Cooper et al,[19] determined the excretion of the 10 "essential" amino acids, by microbiological techniques, in 6 cases of Wilson's disease. They found an absolute increase for all amino acids studies over the normal values, with the largest absolute and percentage increase in threonine. Serine was not determined by them.

Our case was that of J.T., a 19-year old girl, who on 3 occasions had shown urinary alpha amino nitrogens of 213, 241 and 335 mg/24 hrs. The last specimen was the one used for chromatographic studies. The plasma amino nitrogen level was a normal 4.9 mg %. In paper chromatographic studies on the urine, not more than a trace of taurine and no aspartic acid were detected. Free glutamic acid was present. In terms of mg per 24 hrs. there was an increase over normal in all peaks, varying from 1.3 times for valine to 4.9 times for alanine-glutamic acid. This latter increase is due partially at least to the presence of free glutamic acid. Table V gives the results on the free amino acids in terms of percentage distribution. The outstanding abnormality is in the increased threonine excretion, for here this peak does not contain taurine. Serine did not separate from glycine in the unhyrolyzed chromatogram, but after hydrolysis serine was present in a normal proportion. It is safe to assume then, that serine was not present in an abnormally high proportion in the free form.

Table V

Free Urinary Amino Nitrogen in Wilson's Disease

Peak	% of total amino-N
Leucine - isoleucine	1.8
Valine	0.6
Tyrosine - methionine	2.1
Alanine - glutamic acid	12.2
Threonine	12.0
Serine - glycine - glutamine	44.8
Lysine	6.5
Histidine	18.6

After hydrolysis, there was an increase of only 30% in alpha amino nitrogen, and there appeared to be only small amounts of combined glycine present.

There are thus marked similarities between our cases of Fanconi syndrome and Wilson's disease. In addition to the gross aminoaciduria, both show essentially no taurine, markedly increased threonine and little combined glycine. They differ in that a disproportionately large amount of serine was excreted by the Fanconi syndrome patient and not in Wilson's disease. The unusually large excretion of threonine in Wilson's disease is in agreement with the findings of Cooper et al.[19]

Post-necrotic cirrhosis.

Although the liver is so central in amino acid metabolism it is only in extremely severe liver disease that gross disturbances are evident. With the newer techniques it is possible to look for more subtle abnormalities in the less destructive forms of the disease. Determining from 3-15 amino acids by microbiological techniques Dunn et al[29] studied the urines of 25 patients with different types of liver disease. They found many abnormalities, both increases and decreases, but no obvious consistent pattern emerged from their study. Eckhardt et al[3] studied 7 patients with severe liver disease and found, with the microbiological technique, no significant differences from normal as far as the urinary amino acids were concerned. With paper chromatography Dent[30] has observed certain abnormalities. He has listed 6 types of urinary amino acid changes from normal, including excess amounts of cystine, beta-aminoisobutyric acid, methyl histidine and ethanolamine, in various combinations.

Our case was that of a 17-year old girl with post-necrotic cirrhosis. Her total urinary alpha amino nitrogen was 153 mg/24 hours. By paper chromatography the unhydrolyzed urine showed almost no threonine, no free glutamic or aspartic acids, an unusually intense tyrosine spot and more than the usual number of unidentified spots. Table VI contains the quantitative results in terms of % total amino nitrogen. There is a slight increase as compared with the normals in leucine-isoleucine and in valine - tyrosine - methionine. In the hydrolysate valine is present as a separate peak, and here it is the tyrosine-methionine peak which is somewhat elevated. Presumably the same relative distribution is true in the unhydrolyzed sample. The results on paper suggest that tyrosine is present in larger amounts than in the normal. The outstanding abnormality is the presence of a rather conspicuous unidentified peak which we now refer to as "blue proline." It emerges at a point practically identical with proline, but gives a blue color with the ninhydrin reagent whereas proline gives a red color. This peak made up 6% of the total amino nitrogen. A comparable component has been seen only in one other of the 11 urines studied, and that was in a normal urine where it was present in smaller amounts, making up 3% of the total. "Blue proline" is acid stable since it was present in the hydrolyzed urine in an amount identical with that in the unhydrolyzed specimen. The identity of this peak with one of the unknown spots on paper has not yet been established. The peak can be readily isolated for purposes of further characterization and possible

Table VI

Free Urinary Amino Nitrogen in Post-necrotic Cirrhosis

Peak	% of total amino-N
Leucine - isoleucine	3.5
Valine - tyrosine - methionine	4.9
"Blue proline"	6.0
Alanine	4.7
Threonine - taurine	12.0
Serine - glycine - glutamine	39.1
Lysine - "pre-lysine"	12.7
Histidine	17.2

identification. The detection of "blue proline" emphasizes one advantage of the starch column technique over the microbiological, in that such a component would not be detected by the latter method. Also the component can be much more readily isolated than would be the case using paper chromatography.

No abnormalities in the hydrolyzed urine were observed other than the presence of "blue proline."

Acute Yellow Atrophy of the Liver

Incomplete studies were made on the urine of a 5-year old boy who subsequently died and showed at autopsy acute yellow atrophy of the liver. He showed a markedly elevated blood alpha amino nitrogen level (17 mg%) and gross aminoaciduria (243 mg. alpha amino nitrogen /24 hrs; 9.7 mg. per kg. body weight per 24 hours). The outstanding feature was the presence of unusually large amounts of combined amino acids. After hydrolysis, alpha amino nitrogen was increased 4.4 times. A starch column chromatogram revealed that the alanine-glutamic acid peak made up about 50% of the total amino nitrogen in the hydrolysate and that the greater part was composed of glutamic acid. One can only speculate that the amino group of glutamic acid becomes conjugated in some tissue other than the liver, and that the liver normally acts in some way to dispose of a large part of this compound.

Fourth case.

This was a 6-year old boy, J.B., with known heart disease since the age of 4. He had an enlarged heart, and episodes of heart failure. His condition was aggravated by low serum proteins (for example, total protein 3.3 gms %, albumin 1.0 gms %), which were not raised by long periods of tube-feeding with a high protein intake. He was studied because of the possibility that there might be excessive losses into the urine of some amino acids.

Two different urine specimens were run, 3-months apart in collection, and they contained 59 and 42 mg. alpha amino nitrogen per 24 hours. From paper chromatography it was learned that threonine was absent, or present in only very small amounts, in both specimens. Both specimens showed also, when run on starch columns, a lower excretion per 24 hours for each component as compared with normal adults. On a percentage basis, one specimen showed a high proportion of taurine while the other showed abnormally high proportions of lysine and histidine. On hydrolysis of one specimen, there was an increase of 2.6 times in alpha-amino nitrogen over that of the unhydrolyzed sample. The results are considered to be non-contributory as far as the etiology of the hypoproteinemia is concerned.

Diabetes mellitus

In diabetic coma the levels of amino acids in the plasma and in the urine are increased above normal.

The case studied was that of a woman admitted to the hospital in coma. The urine was obtained 3 days after admission and after the administration of insulin, but while the patient was still markedly hyperglycemic and glycosuric.

The total alpha amino nitrogen was 80 mg. per 24 hours. The most marked abnormalities were low relative concentrations of serine and histidine. After hydrolysis there was an increase of 2.4 times in alpha-amino nitrogen.

The significance of the findings is not known.

Summary

(1) Urinary alpha-amino nitrogen has been determined in 10 normal adults and in 22 patients with various diseases.

(2) Chromatograms obtained by elution from starch columns of urine from 6 normal subjects and 5 patients

have shown the presence of 10 major peaks containing amino nitrogen. The components of the peaks have been fairly completely established.

(3) The normal subjects showed a fairly consistent urinary amino acid pattern, while the urines from the 5 patients all showed deviations from the normal.

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II. MEDICAL SCHOOL NEWS

Coming Event

June 23-28 Continuation Course in Otolaryngology for Specialists

* * *

Dr. Rasmussen To Retire

Faculty and students, alike, will miss Dr. A. T. Rasmussen who retires on June 15 after 36 years of distinguished service in the Department of Anatomy.

Doctor Rasmussen was born in Spring City, Utah, of Danish stock, and for a time in his youth served as a sheep herder. After obtaining the degree of Ph.D. in physiology from Cornell University, he came to Minneapolis in the fall of 1916, as instructor in Neuroanatomy. By 1925 he had been advanced to a full professorship in the department. Soon he became known as an authority on the antomy of the pituitary gland and as one of the leading neuroanatomists in the country. In 1923 and 1936 he served as vice president of the Association for the Study of Internal Secretions, and in 1948 as a vice president of the American Association of Anatomists. In addition to numerous contributions to medical publications, he is the author of several books of his own of which "The Principal Nervous Pathways" is perhaps the best known. Since 1946 he has been a regular contributor to the annual review, "Progress in Neurology and Psychiatry".

In this school he will long be remembered for his conscientious service as chief examiner and as one of the most inspiring and competent teachers in the basic sciences. The best wishes of the staff go with Dr. and Mrs. Rasmussen to California, the new Promised Land.

* * *

Dr. Flink to Succeed Dr. Ebert at Veterans Hospital

Dr. Edmund B. Flink, Associate Professor of Medicine, has been appointed Chief of Medicine at the Minneapolis Veterans Hospital, succeeding Dr. Richard V. Ebert, who will become the new Clark Professor of Medicine at the University. Dr. Flink will assume his new post July 1. His abilities as clinician and teacher are well-known to his associates and former students who join in extending their best wishes to him in his new position.

* * *

Minnesota State Medical Association Meeting

The 99th annual meeting of the Minnesota State Medical Association will be held in Minneapolis on May 26, 27, and 28. An outstanding program has been arranged covering scientific subjects of interest both to the specialist and to the general practitioner. Thirty-two scientific exhibits and over 100 technical exhibits will be presented in the Minneapolis Auditorium.

* * *

Faculty News

Several members of the Department of Pediatrics recently attended a meeting of

the Society for Clinical Investigation at Atlantic City, New Jersey, and the meetings of the Society for Pediatric Research and the American Pediatric Society at Old Point Comfort, Virginia. Doctors Lewis Thomas and Floyd Denny presented a paper on "The Demonstration of Type-Specific Streptococcal Antibody by a Hemagglutination Technique Employing Tannic Acid," and Dr. Charles D. May spoke on "Infection as a Cause of Folic Acid Deficiency and Megaloblastic Anemia: Experimental Induction of Megaloblastic Anemia by Turpentine Abscess." Dr. Forrest Adams discussed "Studies on the Nonspecific Hyaluronidase Inhibitor in the Blood of Siblings and Parents of Children with Rheumatic Fever," and Dr. Charles Stewart presented a paper entitled, "On the Role of Ascorbic Acid in the Function of the Adrenal Cortex." Dr. Irvine McQuarrie, Professor and Head, Department of Pediatrics, was elected President of the American Pediatric Society. The faculty joins in congratulating Dr. McQuarrie on this well-deserved recognition.

Dr. J. L. McKelvey, Professor and Head, Department of Obstetrics and Gynecology, attended the recent meeting of the American Gynecological Society at White Sulphur Springs, Virginia. He participated in a debate on the subject of carcinoma In Situ.

On May 16, Dr. David Glick, Professor of Physiological Chemistry, presented a seminar on "Recent Trends in Histochemistry" at the Chemical Corps Medical Laboratories, Army Chemical Center, Maryland.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

May 26-31, 1952

Monday, May 26

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom, Todd Amphitheater, U. H.

11:30 - Physical Medicine Seminar; Teaching Aids in Occupational Therapy; Borghild Hansen; Eustis Amphitheater, U. H.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - Physiology Seminar; Electro-Architectonic Mapping of the Cerebral Cortex; Berry Campbell; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Seminar on Fluid and Electrolyte Balance; Todd Amphitheater, U. H.

4:00 - Pediatric Seminar; Juvenile Diabetes; Margaret Huelskamp; Sixth Floor West, U. H.

4:30 - 5:30 Dermatological Seminar; M-346, U. H.

4:30 - Public Health Seminar; 15 Owre Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

7:30 - Fracture Grand Rounds; Dr. Zierold; Sta. A.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Monday, May 26 (Cont.)

Ancker Hospital

8:30 - 10:00 Chest Disease Conference.

1:00 - 2:00 Medical Grand Rounds.

Veterans Administration Hospital

8:00 - 9:00 Neuroradiology Conference; B. J. O'Loughlin, R. C. Gray; 2nd Floor. Annex.

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; B. J. O'Loughlin; Conference Room, Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; C. K. Aldrich; Bldg. I.

Tuesday, May 27

Medical School and University Hospitals

8:30 - Conference on Diet Endocrines and Cancer; M. B. Visscher; 116 Millard Hall.

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Veterans Hospital Staff; Drs. Fink, O'Loughlin, et al; Eustis Amphitheater, U. H.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

8:30 - 9:30 Medical-Roentgenology Conference; Auditorium.

1:00 - 2:30 X-ray-Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

Tuesday, May 27 (Cont.)

Minneapolis General Hospital (Cont.)

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael, and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; L. J. Hay, B. J. O'Loughlin; Conference Room, Bldg. I.

1:00 - Surgery Chest Conference; T. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Wednesday, May 28

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Norman Jacob and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Radioisotope Seminar; Speaker and Subject to be announced; 111 Owre Hall.

12:30 - 1:30 Permeability and Metabolism Seminar; Nathan Lifson; 129 Millard Hall.

1:30 - Conference on Circulatory and Renal System Problems; M. B. Visscher; 116 Millard Hall.

Wednesday, May 28 (Cont.)

Medical School and University Hospitals (Cont.)

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

7:00 - 8:00 Dermatology Journal Club; Dining Room, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

2:00 - 4:00 Medical Ward Rounds;

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

8:00 - Pediatric Allergy Rounds; Lloyd Nelson; 4th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

1:30 - Pediatric Rounds; E. J. Huenekens and Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, May 29

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

Thursday, May 29 (Cont.)

Medical School and University Hospitals (Cont.)

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

3:30 - Medicine-Pediatric Infectious Disease Conference; Heart Hospital Auditorium.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 Radiology Seminar; Studies of the Growth of Transplanted Mouse Adenocarcinoma as Affected by Peripheral Irradiation of the Tumor Bed; Dale Parshall; The Effect of Pre-Irradiation of the Tumor Bed on the Transplantation of Tumors; Harvey Stone; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hours; 206 Temporary West Hospital.

Ancker Hospital

4:00 - Medical Pathological Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

8:30 - Neurology Rounds; William Heilig; 4th Floor.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

1:00 - Fracture-X-ray Conference; Dr. Zierold; Classroom.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; B. J. O'Loughlin; Conference Room, Bldg.I.

Friday, May 30 (HOLIDAY)

Saturday, May 31

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

Saturday, May 31 (Cont.)

Medical School and University Hospitals (Cont.)

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; Brain of Sorex Cinereus; Maria F. Ryzen; Distribution of Potentials in the "Optic" Cortex; Nathaniel A. Buchwald; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; George Lund; 5th Floor.

11:00 - 12:00 Medical-X-ray Conference; O. Lipshcultz, Thomas Lowry, and Staff; Main Classroom,

11:00 - Pediatric Clinic; C. D. May and Floyd Denny; Classroom, 4th Floor.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Benstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.