Utilization of Proteins

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Research is increasing our understanding of the biochemistry and metabolism of amino acids. The resulting body of knowledge points the way to better human and animal nutrition

THE HUMAN BODY contains an infinite variety of specific proteins. The bulk are integral components of such rigid or semirigid tissues as the muscles, skin and nails, the brain, and the bones and teeth. Others function as hormones or enzymes, or in numerous other capacities. In common with other nitrogenous, but nonprotein substances, all body proteins are derived ultimately from the nitrogen provided in the diet in the form of animal or vegetable protein.

It is by now well established that the capacity of a protein to promote growth, or to offset loss of nitrogen in the adult, depends essentially upon the adequacy with which the quantity and proportions of the various amino acids produced by digestion and absorption match the quantity and proportions needed for tissue synthesis or repair. It seems obvious that animal proteins should do this better than vegetable proteins, as is indeed the case. About half of the 20 or so amino acids yielded in the hydrolytic breakdown of the average protein can be synthesized by the body from other dietary components, but the other half are "essential" in the sense that when they are omitted from the diet, whether by design or by accident, the body is unable to compensate adequately for their lack by manufacturing them from substances normally present. As a consequence, effective fabrication of new protein is prevented even though ample amounts of all of the other amino acids needed for this purpose be present.

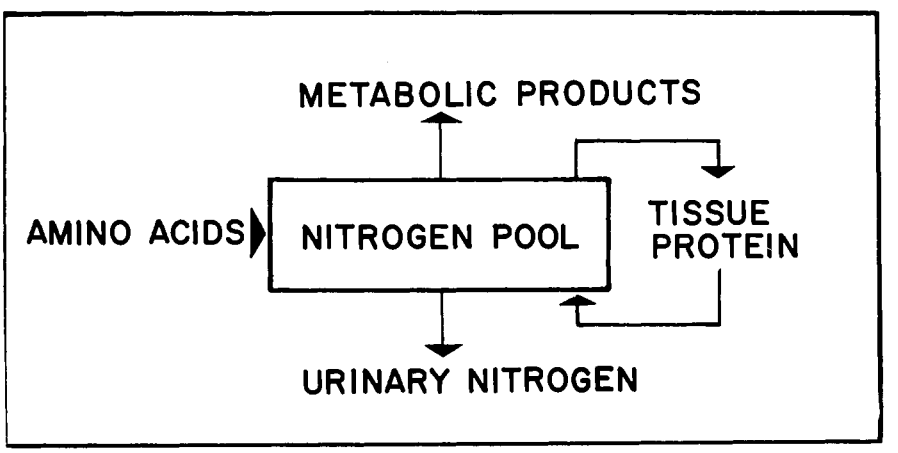
The term "essential" or "indispensable" must be defined with reference to the physiological need to be met and the animal species concerned. The young animal must build much new tissue, whereas the adult's primary need is to keep tissue already built in good repair. The young rat is able to grow when arginine is omitted from its diet, though not at a maximal rate. The adult rat maintains itself as well on a diet devoid of arginine as on one which contains it. Hence in this species arginine can be said to be essential for growth but not for maintenance. The adult rat must have a source of dietary histidine for its maintenance. Curiously, the adult human male requires neither dietary arginine nor dietary histidine.

Pioneer tests of amino acid mixtures, begun by Rose and his students in the rat and dog, have now been extended to include determination of the quantities of the essential amino acids needed by the human adult. The table on page 576 summarizes conclusions based on the assays made in the adult human male fed diets which provided all nonprotein components in ample amounts but contained mixtures of amino acids instead of protein.

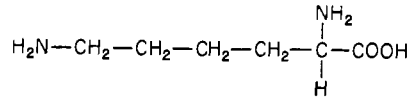
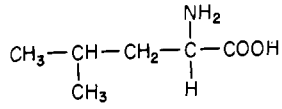
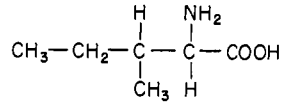
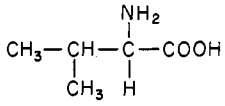
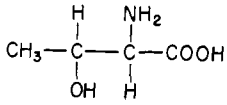
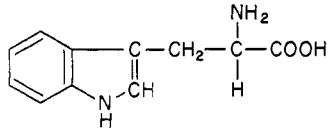
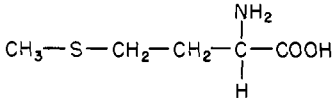
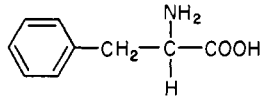
It is important to emphasize that the nonessential amino acids are dispensable only because they can be provided by synthesis in the body from other amino acids or other substances. Addition of the nonessential amino acids to a basal diet containing moderate amounts of the essential amino acids promotes better growth in the experimental animal than is obtained when the basal diet is not thus fortified. Some benefit is also derived when ammonium citrate is added as a source of extra nitrogen for nonessential amino acid synthesis. When only the essential amino acids are provided, a part of these must be diverted for such synthesis.

It is interesting to note that the adult male subject subsisting on a diet which provides free amino acids in the form of essential amino acid mixtures or of protein hydrolyzates, in lieu of the usual protein, must have a high caloric intake if he is to utilize these amino acids effectively for maintenance of nitrogen equilibrium. The reasons for this are uncertain. Hydrolysis of simple peptides is known to release energy, the synthesis of peptides to require its addition. In the microörganism there is some indication that peptides of certain of the essential amino acids are somewhat more effective in promoting growth than are

Human feeding tests have demonstrated that the essential amino acids enter into the metabolic nitrogen pool which in turn is the source of the almost infinite variety of proteins which make up the human body



Minimum Essential Amino Acid Intakes (Strictly Tentative) for Normal Man When Diet Furnished Sufficient Nitrogen for Synthesis of Non-essentials

Amino Acid[a]	*Formula*	*Minimum Daily Requirement*[b]
L-Lysine		0.80 gm.
L-Leucine		1.10 gm.
L-Isoleucine		0.70 gm.
L-Valine		0.80 gm.
L-Threonine		0.50 gm.
L-Tryptophan		0.25 gm.
L-Methionine		1.10 gm.
L-Phenylalanine		1.10 gm.

[a] The D forms of the first six amino acids listed will not replace the L forms in the diet of the normal man. D-Phenylalanine is partially utilizable for this purpose, D-Methionine readily so.
[b] The recommended allowance is twice the minimal.

The following amino acids have been shown to be non-essential in the adult human male:

Glycine	Tyrosine	Hydroxyproline
Alanine	Aspartic Acid	Histidine
Serine	Glutamic Acid	Arginine
Cystine	Proline	Citrulline

the free amino acids which they contain. Whether this may be a factor, or not, in the human subject, one can only speculate.

Tissue Proteins in Equilibrium

The idea that the tissue proteins are in equilibrium with each other, with the proteins and amino acids in the body fluids, and to some extent also with other nitrogenous compounds, has by now become generally accepted. Use of the terms "endogenous" metabolism and "exogenous" metabolism in their original absolute sense as constituting two distinct metabolic pathways, the first involving synthesis and maintenance of body tissue and the second the catabolism of excess dietary protein, has therefore been invalidated. The endogenous and exogenous pathways exist rather as currents in a common "metabolic nitrogen pool." Through the intercommunication afforded by the various body fluids, amino acids provided by the tissues become indistinguishable from those provided by the diet. Amino acids from both sources are withdrawn for the synthesis of new protein, for the production of metabolites, to provide energy, or for such other purposes as need may direct. Dietary protein must be provided daily if the tissues are to be properly maintained. When the diet fails to replenish the pool, the tissues are called upon to step up their various contributions. When increased levels of good quality proteins are fed, there is a tendency for the tissue proteins to increase somewhat in quantity over the amount present when the dietary protein content is lower. This is as might be expected in an equilibrium system. No special type of storage protein is known.

Few Facts Known about Mechanism of Protein Synthesis

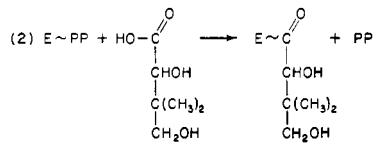
As to the mechanism of protein synthesis, one can at present only speculate from the few facts which are known. The structural specificity of a protein is probably conveyed primarily by the proportions and periodicity of arrangement of the amino acids which comprise it. The curious fact is that in a given tissue of an individual organism the same specific type of protein (with few exceptions) is produced and reproduced as in the analogous tissue of all other individuals of the same species.

The production of antibodies as components of the gamma globulin fraction of the blood, when antigens are administered, affords a possible clue. The antigen somehow leaves its imprint on the gamma globulin fraction, perhaps during its period of fabrication, so that a portion of this globulin fraction will subsequently react readily with an antigen of the same type. In an analogous manner, one or several of the enzymes presumably involved in the synthesis of a specific protein may possibly act as templates or in some other way to determine the amino acid pattern in the peptide chain.

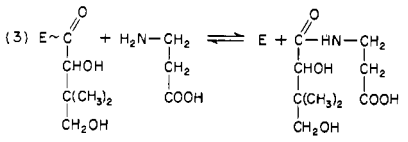
Lipmann has proposed a model cycle for polypeptide synthesis which is based upon a study of the synthesis of pantothenic acid from pantoic acid and β-alanine. In the latter, the enzyme (E) is pictured as first being activated by combining with pyrophosphate (PP) furnished by adenosine triphosphate ($Ad\text{-}PPP$):

(1) $E + Ad\text{-}P\sim PP \rightleftharpoons E\sim PP + Ad\text{-}P$

The pyrophosphate is then exchanged by the enzyme for pantoic acid:



The pantoyl group, thus activated, combines with the amino group of β-alanine to produce pantothenic acid and release the enzyme:

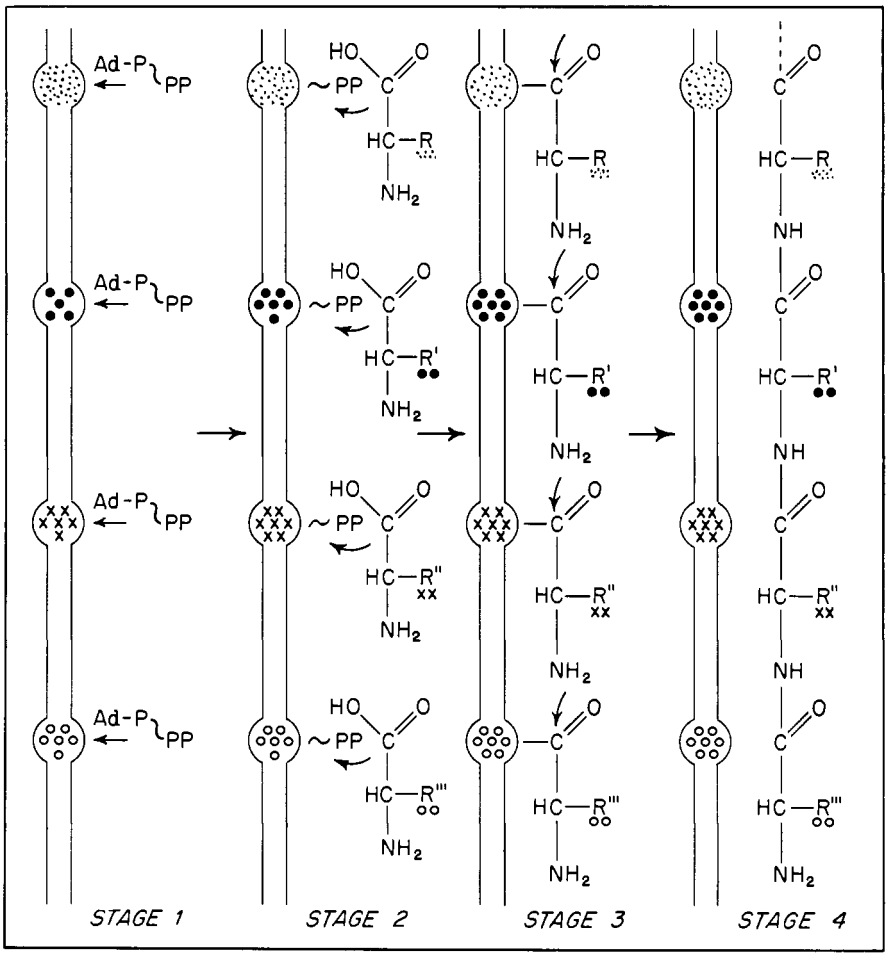


In the model cycle proposed for protein synthesis the enzyme involved is assumed to be provided with activation centers lined up in definite sequence, each capable of activating a specific amino acid. Each such activation center (Stage 1) is assumed to be energized by combination with pyrophosphate supplied by adenosine triphosphate (Stage 2). The pyrophosphate groups are in turn exchanged for the acyl groups of the specific amino acids, to provide a series of amino acids in definite sequence, each with an activated carboxyl group in close proximity to the amino group of its adjacent amino acid (Stage 3). Condensation then forms a polypeptide chain with its pattern determined by the enzyme and frees the enzyme to repeat the cycle (Stage 4).

The energy needed for the synthesis of the peptide bond is less than that provided by the adenosine triphosphate. The surplus is assumed to be available for the mobilization and concentration of the specific amino acids in proper sequence at the active centers on the enzyme. The mechanism proposed is attractive. That it presents only a small part of the picture in no way detracts.

Possible Role of Nucleoproteins in Protein Synthesis

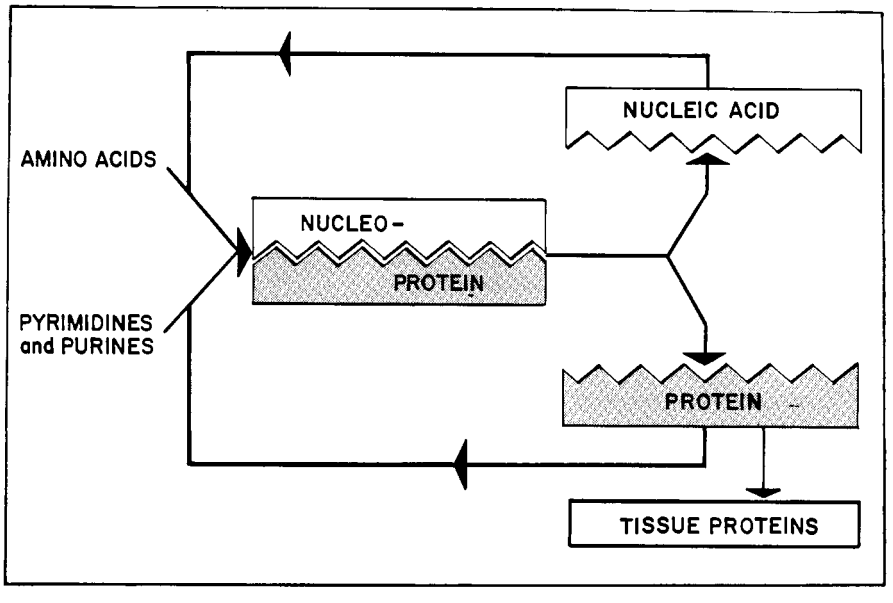
There is considerable speculation in the literature that the synthesis of the simple proteins is dependent upon the presence, or the concurrent synthesis, of the nucleoproteins. The fresh hen's egg contains little or no nucleoprotein and no store of its constituent purines or pyrimidines, but these are produced in increasing amounts during incubation and embryonic development. Chemical study of the chromosomes indicates that they consist largely of nucleoproteins of the desoxyribonucleic acid type (DNA). During active synthesis of protein in the cell, relatively high concentrations of ribonucleic acid (RNA) are found in the cytoplasm. In an in vitro system which contains fragments of bacterial cells biosynthesis of proteins from added amino acids is reported to be stimulated strikingly by the addition of a ribonucleic acid fraction isolated from



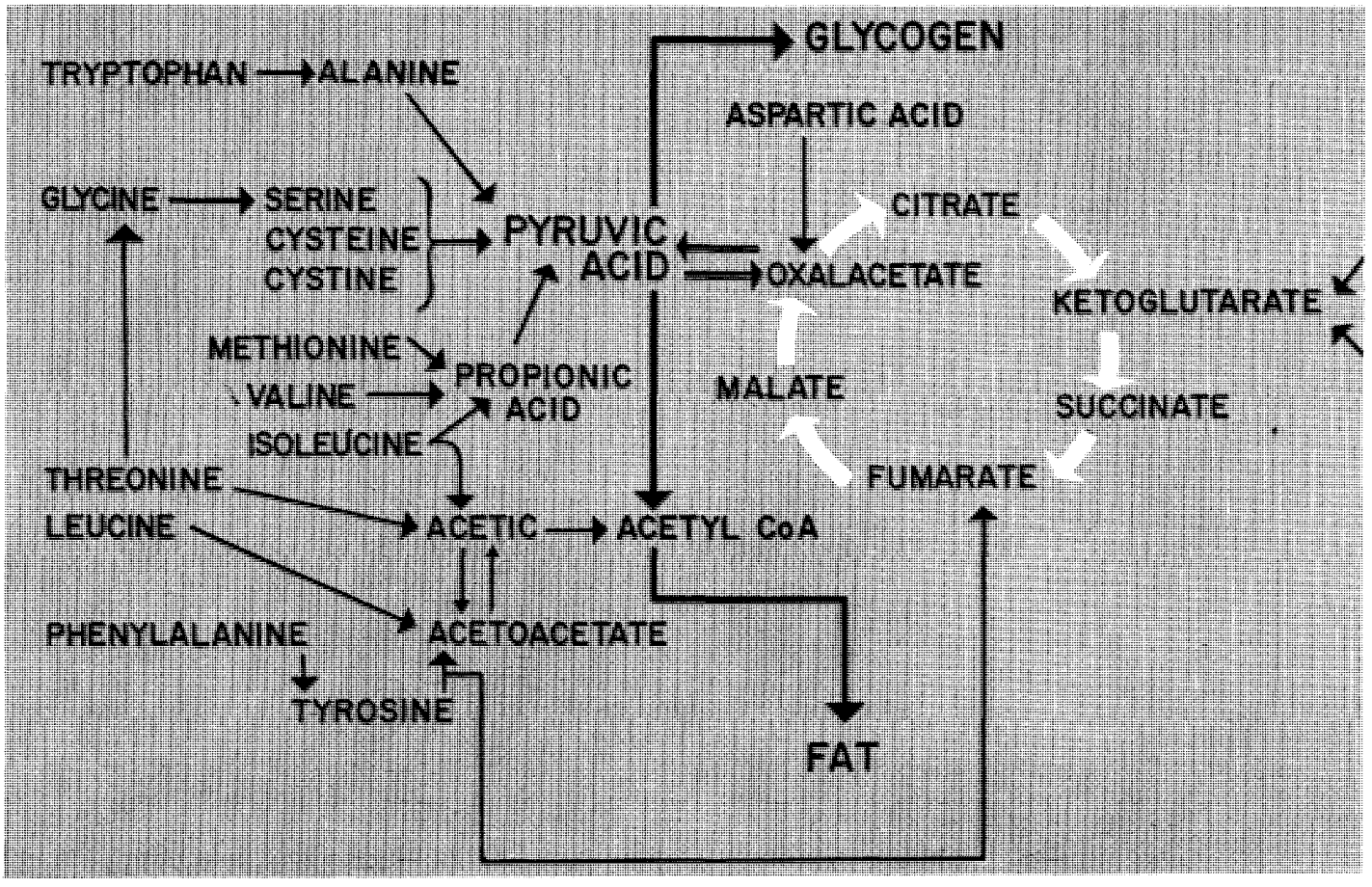
Model by Lipmann explains the biosynthesis of the extremely complex yet precise proteins formed in living systems. The order of amino acids within the polypeptide is assumed to depend upon the order of activation centers on the enzyme

the organism, or even by a mixture of purine and pyrimidine bases.

The reciprocal nature of the synthesis of protein in the presence of purine and pyrimidine bases and the synthesis of nucleic acids in the presence of amino acids may be represented schematically as follows:



The synthesis of nucleic acid from purine and pyrimidine bases and the synthesis of proteins from amino acids are believed to be interdependent. The chromosomes have been found to consist largely of nucleic acid and perhaps the organization of genes on chromosomes provides the organization pattern for proteins



Possibly the impelling argument for some interrelationship is that in the intact organism a definite pattern of development takes place which involves the production of simple and conjugated proteins characteristic of the species. This development is under genetic control and subject to minor modification presumably by variation in the genetic pattern of the chromosomes. Direction is probably given through the evolution of a definite pattern of enzymes, themselves proteins capable collectively of catalyzing biosynthetic reactions.

Synthesis of Purines and Pyrimidines

As has already been intimated, a nucleoprotein consists of two components—a protein combined chemically with nucleic acid. Nucleic acid may be regarded fundamentally as a polymer of an indefinite number of mononucleotide units, each of which contains a molecule of phosphoric acid, a molecule of a pentose (either ribose or desoxyribose), and a molecule of an organic base (either purine or pyrimidine). Quite apart from their existence as components of nucleoprotein, there are numerous examples of nucleotides and quasinucleotides which have independent functions. We have already referred, for example, to the mononucleotide, adenylic acid (or adenosine monophosphate—AMP or *Ad-P*), and its capacity to store energy for subsequent release by combining with additional phosphate units to produce adenosine diphosphate (ADP or *Ad-PP*) or adenosine triphosphate (ATP or *Ad-PPP*).

When adenylic acid is combined with such quasimononucleotides as nicotinamide mononucleotide or flavin mononucleotide, it produces dinucleotides which serve as coenzymes or prosthetic groups which are indispensable in the functioning of certain oxidizing enzyme systems.

The evidence indicates that if ample phosphate is available, the pentose and the organic bases can be produced to complete the synthesis of nucleic acid. Unless this were true, embryonic development within the egg could not occur, nor could the infant subsisting on a diet essentially devoid of pentoses, purines, and pyrimidines develop. The adult has long been known to excrete uric acid—an end product of purine metabolism—even though purines are carefully eliminated from the diet. The purines and pyrimidines are of particular interest because they contain nitrogen and have long been supposed to be derived from the amino acids. This deduction has been verified experimentally by tests involving the use of isotopically marked precursors and the location of the isotopic markers in the isolated purine or pyrimidine molecule. Thus, in adenine, nitrogens 1, 3, and 9 and the 6-amino group have been shown to come from ammonia, which presumably may be most readily produced from glutamine or asparagine or from glutamic or aspartic acid.

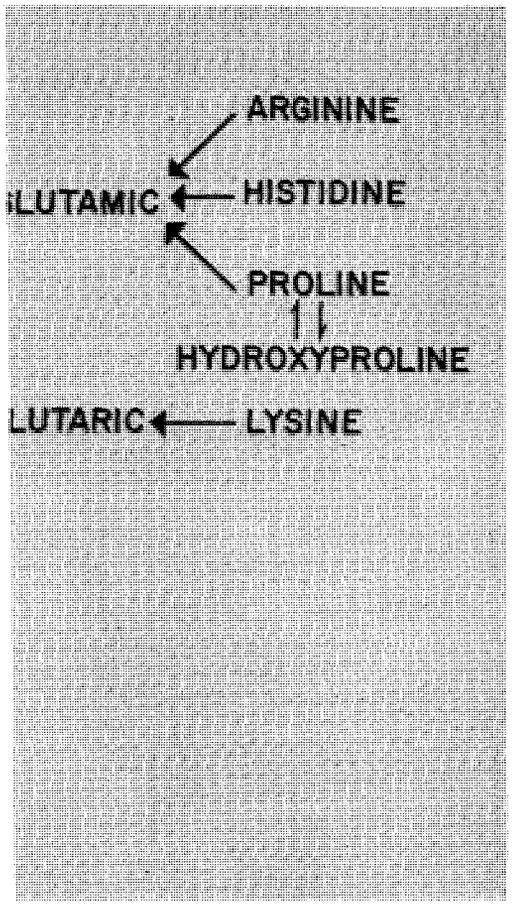
C_4, C_5, N_7 arise from glycine and C_2 and C_8 are formed from "formate," which may be produced from serine (as may also glycine) or from certain other sources. C_6 has its origin in CO_2.

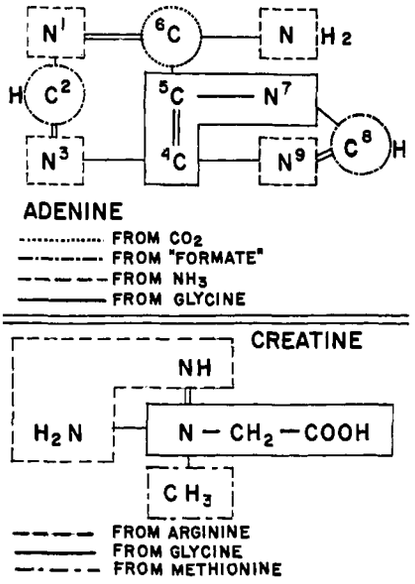
Synthesis of the pyrimidines has not been as well charted as to the origin of each group.

Synthesis of Other Nonproteins

Creatine is another product of importance because of its capacity to store energy by combining with phosphoric acid and to release it again when the phosphate is reconverted to creatine and inorganic phosphate. Like the purines, it need not be provided in the diet. Its origin has been definitely traced by a variety of procedures to the amino acids: glycine, arginine, and methionine.

The nitrogen found in heme, the prosthetic group of hemoglobin, has been shown to be derived from glycine. Various peptides and other products might be added to this list.





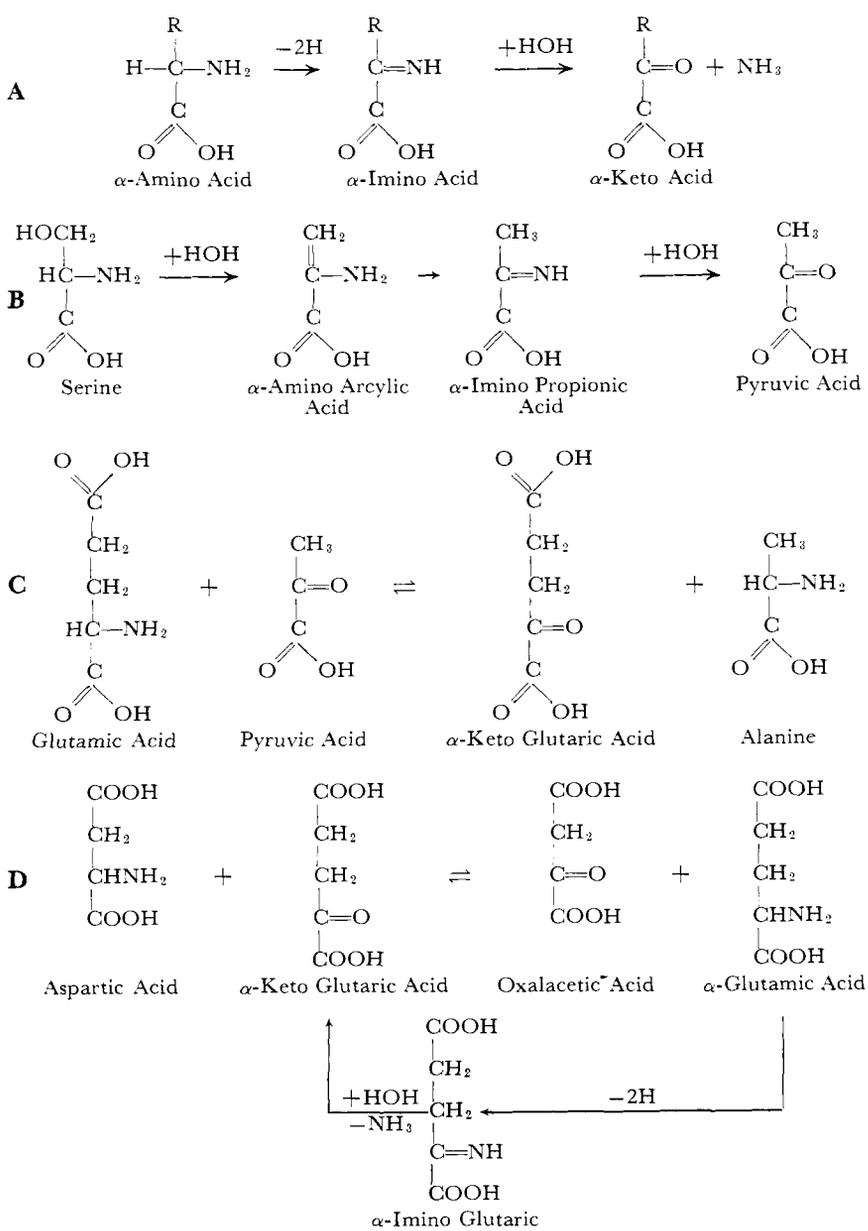
Amino Acids Not Stored

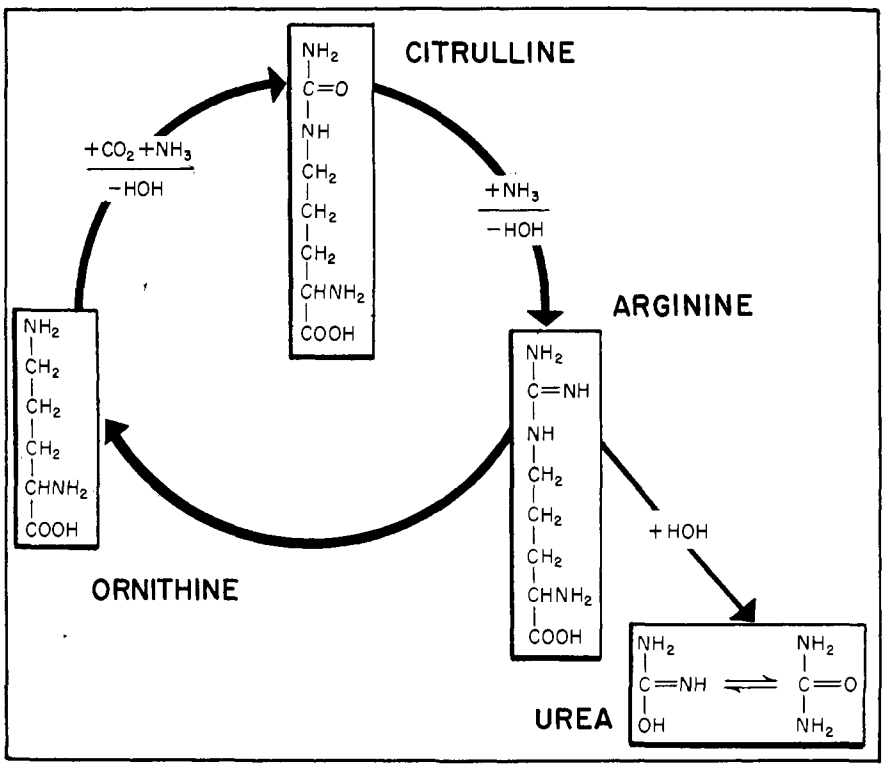
The amino acids which are not withdrawn from the nitrogen pool for synthetic purposes are not stored. They may be broken down to remove the amino nitrogen and leave the carbon skeleton, initially in the corresponding keto acid form. The keto acids may, in turn, be used to provide energy or may be converted into energy-producing carbohydrates or fats. A few of the amino acids, such as histidine, tryptophan, lysine, phenylalanine, and tyrosine, seem to follow uniquely individual paths, at least initially. Space will not permit discussing these variations in detail.

There are at least three mechanisms for removal of the amino group from the α-amino acids. The earliest way suggested was by oxidative deamination. This process has been shown to occur primarily, if not exclusively, in the liver and the kidney. It can be represented in its simplest form by the reactions in the diagram to the right.

The enzyme system which attacks most L-amino acids is known as L-amino acid oxidase, an oxidative dehydrogenase which removes hydrogen from the amino acid and ultimately transfers it to oxygen. L-Amino acid oxidase consists of a protein and specific prosthetic group (a quasi-mononucleotide, riboflavin-phosphate). The riboflavin in the nucleotide "accepts" the hydrogen and undergoes reduction. On contact with oxygen, it is reoxidized and the oxygen is converted to hydrogen peroxide. The latter is decomposed to water and oxygen by catalase, an enzyme which is widely distributed in the tissues. Once formed, the α-imino acid decomposes spontaneously in the presence of water to form ammonia and the α-keto acid (A). Some oxidatively deaminizing enzyme systems contain coenzymes which transfer the hydrogen which they remove to a more complicated hydrogen-transport system.

With amino acids which contain a β-hydroxyl (serine or threonine) or a β-sulfhydryl (cysteine) group, nonoxidative deamination may occur (B). Here the reaction involves the removal of water or of hydrogen sulfide to produce the corresponding α, β-unsaturated amino acid, which rearranges to the





A simplified explanation of urea formation in humans. This mechanism provides for the removal of ammonia formed by oxidation of amino acids

α-imino acid. This then undergoes hydrolysis to yield the α-keto acid. Threonine is converted to α-keto butyric acid. Serine and cysteine yield pyruvic acid, a key intermediate in the metabolism of carbohydrates, capable of being converted to glycogen or fatty acids or of being oxidized via the tricarboxylic acid cycle.

Enzymes effecting these changes have been found in animal tissue, primarily the liver.

The third type of deamination is known as transamination. Enzymes which effect this type of change are very widely distributed among the tissues. As the name indicates, the reaction involves the transfer of an amino group from an amino acid to a keto acid, with the conversion of the amino acid to a keto acid and of the keto acid to an amino acid. Usually glutamic acid or α-ketoglutaric acid is involved (C, page 579).

It is quite possible that amino acids which are not attacked by known L-amino acid oxidases, such as aspartic acid, may be deaminized in this way and the glutamic acid formed in the process then be oxidatively deaminized to restore the α-keto glutaric acid (D, page 579).

In the process of transamination vitamin B_6 seems to play an essential role. It has been pictured as combining, in the form of pyridoxal phosphate, with an amino acid to produce a conjugate which then yields pyridoxamine phosphate and the keto acid, the pyridoxamine phosphate being subsequently transaminated with α-ketoglutaric acid to yield pyridoxal phosphate and glutamic acid. There is even some indication that the restoration of the pyridoxal phosphate could possibly occur by spontaneous oxidation of the pyridoxamine phosphate.

These and other recent studies, too involved to recount here, have raised the question as to whether transamination may not be much more generally functional than earlier supposed, possibly enough so as to make it the most important of the mechanisms for the deamination of the L-amino acids. However, present evidence does not favor the possibility that the D-amino acids undergo transamination. Potent D-amino acid oxidases, which attack most, but not all of the D-amino acids, have been found in the liver and the kidney.

Urea Formation

In the human subject, and mammalians in general, urea accounts for the bulk of the urinary nitrogen. The ingestion of ammonium salts, particularly the salts of organic acids, as well as the ingestion of proteins leads to its increased production and excretion. The first plausible suggestion as to its mode of formation, via the amidination of ornithine to produce arginine and the hydrolysis of the latter to complete the cycle, was suggested by Krebs on the basis of liver slice studies. In its simplest form, the process may be illustrated as follows:

The cycle consists of three steps, involving (Step 1) the conversion of ornithine to citrulline by the addition of CO_2 and NH_3, (Step 2) the addition of a second molecule of NH_3 to produce arginine, and (Step 3) the hydrolytic cleavage of arginine to yield urea and ornithine.

Recent evidence indicates that the process is actually much more complicated than outlined, involving the production of complex intermediates in Steps 1 and 2 and the participation of ATP, of a derivative of glutamic acid, and of aspartic acid, with the production of fumaric acid in addition to arginine.

In the mammal ammonia is extremely toxic. The concentration found in the blood is exceedingly small. As has already been indicated, a considerable quantity is converted to urea in the liver. A possible pathway for the removal of ammonia produced in the extraphepatic tissues, which are apparently unable to synthesize urea, is through conversion of the ammonia to glutamine. Glutamine is present in the blood and is widely distributed in animal tissue, as is also the enzyme glutaminase needed to synthesize it.

$$HOOC{-}CH_2{-}CH_2{-}CHNH_2COOH +$$

Glutamic acid

$$NH_3 \xrightarrow{-HOH} H_2N{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}CH_2{-}CHNH_2COOH$$

Glutamine

The bulk of the ammonia found in the urine is manufactured for excretion in response to the need of the organism to regulate the "acid-base" or "anion-cation" balance in the body fluids. The normal human subject who ingests acids which must be excreted via the kidney, who ingests foods which yield such acids in their metabolism, or who produces more organic acids than he can oxidize (for example: lactic acid in exercise or acetoacetic acid and β-hydroxybutyric acid in fasting) manufactures ammonia as an expendable alkali in the uriniferous tubules of the kidney. The ammonia combines with H^+ to produce NH_4^+ which is then excreted, along with the foreign or the excessive anions, instead of Na^+, K^+, or Ca^{++}, e.g., which it is expedient to conserve. When the diet is alkali-forming, or when alkalies are ingested separately, the need of such exchange is less and, as a consequence, little or no ammonia is produced. Basically, the over-all mechanism is one which aids in the maintenance of the pH of the tissues within its usual narrow normal limits.

Present evidence indicates that urinary ammonia has one of two origins. Part of it may be produced by the enzymatic hydrolysis of glutamine, part

of it by the deamination of amino acids. Since, in either event, the ammonia has its ultimate origin in the amino acids, any increase in urinary ammonia is accompanied by an equivalent decrease in the urea output, and any decrease in ammonia by an equivalent increase in urea. In this connection it would be unfair to leave the impression that urea cannot, under any circumstances, serve as a source of nitrogen, once it has been produced metabolically. In the ruminant, feeding urea as a source of nitrogen for protein synthesis has been practiced, but in such species the bacteria harbored in the rumen act as the effective symbiotic agent. In the omnivorous animal (the rat) supplementation of an essential amino acid diet with urea promotes improved growth, probably because the urea nitrogen is utilized in part for the synthesis of the nonessential amino acids. Here also the intervention of the intestinal bacteria is a possibility, but isotopic studies have shown that when urea marked with N^{15} is injected, some of the N^{15} can be found in the tissue proteins, and when urea marked with C^{14} is injected, some of the C^{14} is expired as $C^{14}O_2$.

Keto Acid Utilization

One of the most interesting series of developments in the field of amino acid metabolism has been the confirmation of earlier proposed pathways by newer techniques. In most instances, the use of simplified biological systems (organ slices, homogenates, and partially purified enzymes or enzyme extracts) and of isotopically marked amino acids or their intermediates has permitted amplification and more explicit delineation of evidence based, as before, on the capacity to promote: glycogen or glucose formation, acetoacetate or acetone body production, or the ability to provide acetic acid for acetylation or glycine for detoxication in the intact animal or human subject. Unfortunately, space will permit the presentation of only a broad general outline of this large body of detailed evidence which indicates that, in most instances after deamination of the amino acids occurs, their identities are merged with metabolites common also to the carbohydrates and/or the fats. The over-all pattern is presented in simplified form in the diagram on page 578.

Pyruvic acid functions as the bridge over which the metabolites must pass to produce glucose or glycogen. This keto acid is produced directly, by steps earlier indicated, from alanine, serine, cysteine (or cystine). It may be produced indirectly from glycine, which can be converted to serine and from threonine, which may undergo partial conversion to glycine. Tryptophan yields very little detectable glucose or glycogen, but there is some evidence to support the view that the initial intermediate metabolite formed from tryptophan (kynurenine) may undergo fragmentation to produce alanine as one of its cleavage products. Valine may produce pyruvic acid via propionic acid, which is also formed, along with acetic acid, from isoleucine. There is some evidence that methionine is glycogenic and may possibly yield glycogen via propionic acid.

Pyruvic acid may also be produced from aspartic acid via oxalacetic acid and the latter from glutamic acid via α-ketoglutaric acid and the citric acid (Kreb's) cycle. It may therefore also be produced from histidine, arginine, and proline, which are known to be convertible into glutamic acid, as hydroxyproline may also be. Lysine does not promote the formation of appreciable amounts of glucose. The supposition that it yields glutaric acid has been repeatedly substantiated. Recent evidence indicates that glutaric acid may undergo α-oxidation to α-ketoglutaric acid.

Phenylalanine is converted via tyrosine (and homogentisic acid) to fumaric acid and acetoacetic acid. The latter is formed also from leucine and from acetic acid. Acetic acid is produced as a metabolite from threonine and isoleucine, and can also be formed by the decarboxylation of pyruvic acid.

Acetyl coenzyme A is produced by the interaction of acetic acid or a closely related two-carbon compound and coenzyme A. The acetylated coenzyme is involved in the production of fat from two-carbon fragments. It may also react with oxalacetic acid to produce citric acid in the citric acid cycle. To simplify the schematic representation this reaction has been omitted, as have been also several other details.

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From other recent reviews, the reader may recall that passage through the citric acid cycle involves the loss of carbon dioxide and removal of hydrogen. In other words, the cycle is essentially a pathway by which biological oxidation, not only of carbohydrates and fats, but also of the carbon residues of the amino acids, is effected.

An interesting aspect of protein metabolism is the conversion in vivo of tryptophan to nicotinic acid, the component of the vitamin B complex which prevents pellagra. The exact mechanism by which this is effected has been the subject of intensive investigation. Suffice it to say here that the conversion is apparently very inefficient, some 10 times as much tryptophan as nicotinic acid being required to produce the same effect.

D-Amino Acids in Human Nutrition

In this summary of proteins and amino acids, as they relate to human nutrition, nothing has thus far been said concerning the D-amino acids. Peptides which contain the D-amino acids are not readily hydrolyzed by enzymes. Possibly this is one of the reasons why antibiotics which contain amino acids in the D form are not quickly rendered ineffective.

Several of the amino acids have become available commercially, for use in the fortification of foods to improve their biological value or in the supplementation of protein hydrolysates designed to meet nutritional emergencies. With few exceptions these amino acids are synthetic, hence contain the D isomer, as well as the natural L component. In the free form, many of the D-amino acids can be attacked by D-amino acid oxidase to produce the optically inactive α-keto acid, hence undergo inversion through amination of the latter to the L-amino acid. So far as is known, transamination is not possible. The D forms of four of the essential amino acids (isoleucine, leucine, threonine, and lysine) are apparently unavailable for growth in the rat, D-valine is partially available, and D-histidine more readily so. There are species differences, D-tryptophan, for example, being readily utilizable in the rat, but not in the human adult. D-Valine is apparently not available in the human, D-phenylalanine only partially so. It is probably fair to say that the D-amino acids are somewhat less well utilized metabolically because they must first be inverted. For this reason, and others which would require too much elaboration to develop here, they are much more readily excreted than are the L-amino acids. No clear-cut nutritional inhibition has been attributed to the D-amino acids in the mammal, as is the case with many microörganisms.