

CHAPTER 3

Individuality of Amino Acid Needs

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I. INTRODUCTION

The topic of our discussion is intimately related to the much broader subject of biochemical individuality which has recently been treated in a separate volume (Williams, 1956a). The extremely diverse evidence with respect to the scope and magnitude of the biochemical differences which are to be found in normal human bodies, must be considered as a whole before the significance and importance of any part of the evidence can be properly adjudicated. Thus our relatively meager knowledge about individuality of amino acid needs gains much in significance, when we know that this is only one area, among dozens, in which large differences exist.

The importance of the phenomenon of biochemical individuality rests, like the idea of organic evolution, upon many corroborative evidences, which separately might be disregarded by conservative scholars who are not anxious to incorporate new complexities into their thinking. Cumulatively, however, these evidences are overwhelming and the material which we will present on individuality in amino acid needs gains strength when considered in the light of a large body of other related evidence.

II. GENETIC BASIS FOR INDIVIDUALITY IN NEEDS

The fundamental clear demonstration of gene-enzyme relationships made by Beadle (1945) has been productive of a large volume of research, all of which emphasizes the unity of the biological world and

the extension of genetic concepts to all forms of life. From this extensive investigation we can safely draw the broad conclusion expressed by Wagner and Mitchell (1955a) that "genes exert their effects through control of metabolism." This leads us to conclude that no two individuals can have identical metabolisms unless they have identical inheritance and that each member of the human family has a distinctive metabolism and probably a distinctive amino acid metabolism. If this probability is a reality, we must conclude that each individual has amino acid needs which are quantitatively distinctive. This line of argument has nothing to do with the magnitude of the differences; they may be large or insignificantly small so far as this part of our discussion is concerned.

A most important consideration which bears on our problem is the common occurrence in all forms of life of "partial genetic blocks" (Mitchell and Houlahan, 1946) or their equivalent. As a result of their discovery there has been a substantial modification of our ideas with respect to the nature and character of mutations. It was at first supposed that irradiation, for example, simply cancelled out certain genes, and that the observed metabolic effects were the result of complete destruction, from the functional viewpoint, of these individual genes. It became evident, however, from investigations following the original classic ones that genes may be modified to many different degrees, and that partial impairment is a far more common phenomenon than complete destruction. The first observation with respect to partial blocks or "leaky genes" was that while a mutant strain of *neurospora* was quite unable to grow at 35°C. unless riboflavin was added to its culture medium, the potentiality for synthesizing riboflavin for its own needs was not actually lost. At lower temperatures the potentiality was shown to exist; it had only been impaired or modified. Wagner and Mitchell (1955b) state "It is highly probable that every gene has the potentiality of mutating to a very large number of different states . . . The possibilities may be graded into a spectrum . . ."

This important concept leads one to suppose that the metabolism of a particular amino acid, for example (including both anabolism and catabolism) where a number of different pathways and a larger number of steps are involved, could take place in two individuals in accordance with strikingly different over-all patterns, not because of the lack of specific genes in the make-up of either individual but because of quantitative differences occasioned by the numerous different states in which each of the specific genes can exist.

Genetic considerations such as these, which we cannot discuss in detail, would lead us to presuppose, even before any direct evidence was

at hand, that human individuals would have quantitatively distinctive amino acid needs. How great the distinctive differences might be is another question—one which we could not answer *a priori*.

III. ANATOMICAL AND COMPOSITIONAL BASIS FOR INDIVIDUAL NEEDS

If one typical adult human body has substantially the same make-up as another—with organs and other structures all substantially the same, both as to morphology and chemical composition—then we might suppose that the amino acid needs would be substantially the same for each body. Amino acids are required fundamentally to maintain the proteins in our bodies, and if these proteins are qualitatively and quantitatively about the same it might be supposed that the needs of one body would about duplicate the needs of another.

There is ample reason, however, for supposing that the amino acids needed for the maintenance of one body might be appreciably different from that of another, on anatomical and compositional grounds alone. According to a study of the anatomies of 645 normal male rabbits of the same stock, Wade Brown and co-workers (1926) found that in the group, the organ weights, including endocrine glands, corrected for differences in total body weight, varied from 2.3-fold up to 80-fold! The average variation for the 17 items measured was 14.4-fold; the median variation was 10-fold and there were only two organs, heart and brain, for which the variation was less than 5-fold.

There is ample reason to suppose that the variations in human bodies are of the same order as that observed in rabbits. The concept that a typical body would be approximately average with respect to each organ size is completely untenable (Williams, 1957). On the basis of the different protein make-up of each organ, coupled with distinctive patterns of organ sizes, one would be led to assume that the amino acid needs of individuals would show quantitative variation.

Not only are there wide differences in organ size but there are likewise wide variations in microscopic anatomy (of the blood and bone marrow, for example) which would lead supposedly to some differences in amino acid needs. The fact that each individual has distinctive blood and tissue proteins, as demonstrated by transfusions and transplantation as well as electrophoretic studies, is one which might occasion differences in amino acid needs, but it is not clear that these would be large enough to be significant.

No data are available as to quantitative differences in the total amino acid make-up of human bodies, but there is evidence, which we cannot detail here, that specific proteins, particularly the enzymes and those

hormones which are protein in nature, vary in level through ranges of several fold (Williams, 1956b).

Some enzymes which have to do specifically with amino acid metabolism are also known to vary from one normal individual to another. Arginase activity in erythrocytes varies over at least a 4-fold range from one well person to another (Clark and Beck, 1949), and arginase in the skin varies similarly (Van Scott, 1951). This strongly suggests that arginine, for example, may not enter into metabolism with anything like equal facility in different individuals. Several peptidases in erythrocytes were likewise found to vary among 10 individuals over ranges from 2-fold to 6-fold (Adams *et al.*, 1952). For many enzymes we have no information on the question of inter-individual variation.

A point of view which needs to be brought into this discussion is that amino acid (or other) nutrition is not for "the body as a whole," but rather for every cell, tissue, and organ within our bodies. Specialized cells and tissues have specialized nutritional requirements and we should expect nutritional needs to differ from individual to individual because of differences in the sizes and cellular compositions of the various organs and tissues. It is not by any means preposterous to suppose that some individuals may, because of unusually ineffective machinery for producing a particular protein hormone, have relatively high nutritional needs for crucial amino acids which enter into the composition of that hormone. The specific amino acid requirement might be completely out of line with the actual amount entering the hormone, because the entire metabolic pool in the body might have to be maintained at a relatively high level in order that the limiting organ or group of cells be furnished with a sufficiently high concentration.

It is entirely possible, furthermore, that real competition for specific amino acids may exist between various organs and tissues. It may be that an individual possesses an unusually high requirement for a specific amino acid by reason of the existence of a highly effective mechanism for metabolizing this amino acid in a location well removed from the point where its presence may be a limiting factor for cell activity.

IV. DISTINCTIVE AMINO ACID PATTERNS

What may be regarded as indirect evidence with respect to variability of amino acid needs, is the existence of characteristic concentration patterns of these substances in body fluids.

A. URINARY PATTERNS

By the use of paper chromatography, ascending technique (Williams and Kirby, 1948) it has been found in our laboratories that each indi-

vidual exhibits a highly characteristic urinary excretion pattern with respect to the amino acids which are present in urine in small amounts. In one of a number of studies (Berry *et al.*, 1951), from 13 to 54 samples of urine were collected from each of 6 individuals and analyzed for alanine, glycine, serine, glutamic acid, and lysine. The average values for the different individuals showed a spread of 3-fold, 7-fold, 5-fold, 3-fold, and over 100-fold, respectively, for the 5 amino acids listed. Identical twins included in the group of 6 excreted about the same amounts of each. The maximum ratio between the excretion of the twins was 1.6 and the average variation was about 30%.

In view of the fact that uniformizing the diets did not obliterate the patterns in humans (Thompson and Kirby, 1949; Sutton, 1951) or rats (Reed, 1951) and that they are observed in small babies (Berry and Cain, 1951), there are various possible interpretations of their existence; one is that they are merely reflections of kidney differences—of the possibility that the renal thresholds for individual amino acids vary from individual to individual. The losses to the body, incidentally, are small and there is no substantial wastage. That kidney differences are not alone involved, is indicated by the existence of similar patterns elsewhere in body fluids where kidney thresholds would not be operative. Also pointing in the same direction is the fact that the young woman (1 of the 6 above) who was found to excrete about 19 times as much urinary lysine as another of the same sex, was in a later study found to secrete 10 times as much lysine in her saliva as did the other young woman (Berry, 1951).

The other obvious interpretation of these urinary patterns is that the differences are a reflection, possibly only a dim and distorted one, of genetic differences in the completeness with which various amino acids are used up in the day to day enzyme controlled total metabolism of the individual.

B. SALIVARY PATTERNS

Distinctive patterns with respect to amino acid content are also to be found in the salivas of different individuals (Berry, 1951). When samples of morning saliva (no stimulus to induce its flow) were collected from 9 different individuals and analyzed for 6 amino acids, the following results were obtained (Table I). In 2 cases over 20 samples of saliva were collected from each individual and the distinctiveness of each individual was clearly evident. The most striking difference was that of lysine for which the average secretion (21 and 24 samples, respectively) was 15.0 μg . per milliliter in one case and 1.5 μg . per milliliter in the other.

C. DUODENAL JUICE PATTERNS

Rissel and Wewalka (1952a) applied paper chromatography to the study of the free amino acids in the duodenal juice from 10 well individuals and (1952b) 56 patients with various pathologies including those involving gall bladder and liver, and found each individual exhibited a distinctive pattern. Among the 10 normal individuals certain amino acids, viz., leucine plus isoleucine, valine, alanine, glycine, and serine were generally present but the concentrations varied over a 2.5-fold

TABLE I
SALIVARY AMINO ACIDS (9 INDIVIDUALS)

Amino acid	Range of secretion ($\mu\text{g./ml.}$)	Number of individuals secreting detectable amounts
Aspartic acid	0- 3.3	3
Glutamic acid	0-20	8
Serine	0-12	4
Glycine	0-36	8
Alanine	0-29	8
Lysine	0-15	4

range. Tyrosine, glutamic acid, aspartic acid, lysine, and threonine were almost always present but varied over about a 6-fold range. Glutamine-citrulline, cystine, and arginine, were found in varying amounts in about one-half of the cases; hydroxyproline, phenylalanine, and histidine were seldom present.

D. AMINO ACIDS IN BLOOD

For obvious reasons the determination of small amounts of individual amino acids in blood is difficult and we know of no study in which are recorded repeated determinations on a series of individuals. In Table II are given the ranges in the levels found in the plasmas of 17 fasting males. From these data and taking into account the information regarding other body fluids, it appears probable that each individual tends to maintain a distinctive pattern of amino acids in his blood. This is made more probable by the fact that distinctive patterns of other blood components such as glucose, lactic acid, creatinine, urea, uric acid, sodium, potassium, calcium, and magnesium have been observed, when repeated samples from the same individuals were analyzed (Williams *et al.*, 1955). The earlier finding of Rosahn and Casey (1936) that each of 5 individuals exhibited over a period of a year a distinctive blood morphology, is also in line with this probability.

V. QUANTITATIVE DATA WITH RESPECT TO INDIVIDUALITY IN NEEDS

Since an individual's needs will doubtless vary depending on various factors, including especially the components of the diet, the only data which can be considered crucial with respect to individual differences in amino acid needs are those collected under comparable conditions, generally in the same laboratory.

TABLE II
RANGES IN AMINO ACIDS IN BLOOD PLASMA^a

Amino acid	Range (mg./100 ml.)
Alanine	2.4 - 7.6
Lysine	2.3 - 5.8
Valine	2.5 - 4.2
Cysteine-cystine	1.8 - 5.0
Glycine	0.8 - 5.4
Proline	1.5 - 5.7
Leucine	1.0 - 5.2
Isoleucine	1.2 - 4.2
Arginine	1.2 - 3.0
Histidine	1.0 - 3.8
Threonine	0.9 - 3.6
Phenylalanine	1.1 - 4.0
Tryptophan	0.9 - 3.0
Serine	0.3 - 2.0
Tyrosine	0.9 - 2.4
Methionine	0.25- 1.0
Glutamine	4.6 -10.6
Glutamic acid	0.0 - 1.3
Aspartic acid	0.0 - 1.2

^a From Harold A. Harper, Maxine E. Hutchin, and Joe R. Kimmel, *Proc. Soc. Exptl. Biol. Med.* **80**, 770 (1952).

The first conclusive evidence as to individuality of amino acid needs was found by Rose (1949a). Initially it was supposed that by studying quantitatively the needs of 2 individuals the needs of "man" could be determined. This was found not to be true. In the case of some of the essential amino acids it was found by nitrogen equilibrium studies that results were consistent from one subject to another. In other cases, however, "the quantities found necessary vary as much as 100% in different individuals." In the initial experiments with tryptophan the first 2 subjects yielded approximately identical results; the minimum requirement was tentatively set at 0.15 gm. per day. Later, however, a subject was encountered who required 0.25 gm. per day to maintain equilibrium.

Rose (1952) says "In experiments of this nature one can duplicate the findings in the same individual with remarkable regularity even though the tests are repeated at intervals of many months."

That substantial inter-individual differences in the need for tryptophan exist is further corroborated indirectly by studies on monkeys. Tappan *et al.* (1952) state, "Monkey 528 grew steadily upon the administration of 1 gm. of tryptophan per week, while 2 gm. per week were sufficient for maintenance of weight but supported only very irregular growth in monkey 527. In the case of this animal it was necessary to administer 3 to 4 grams of tryptophan per week for growth to be optimum. The other two animals maintained on tryptophan for extended periods were found to require 1 to 2 gm. per week for satisfactory growth." It is apparent that in a group of 4 monkeys a threefold variation in tryptophan needs was observed under the conditions used.

The minimum and maximum daily amino acid requirements for the maintenance of nitrogen balance in normal adult males, as observed by Rose (1949b) were found to be as follows: L-tryptophan, 0.15–0.25 gm.; L-valine, 0.7–0.8 gm.; L-phenylalanine, 0.8–1.1 gm.; L-lysine, 0.4–0.8 gm.; L-methionine, 0.8–1.1 gm.; L-threonine, 0.3–0.5 gm.; L-leucine, 0.5–1.10 gm.; L-isoleucine, 0.65–0.70 gm. The tryptophan requirements were studied for 31 individuals; the needs for the other amino acids were determined on a lesser number.

It seems obvious that when the variation is as much as twofold or more a larger number of individuals should be tested before an adequate idea of the needs of a population could be obtained. Rose recognized this by stating "allowance must be made for the chance that some individuals might require still larger amounts." No serious attempt was made in these studies to ascertain the exact minimum for any individual; in fact in all such studies the emphasis has been on finding the lowest level that would satisfy all the individuals in the group under observation.

Leverton and co-workers (1956a) have made similar studies on amino acid requirements for nitrogen balance in young women. With respect to threonine they found in a small group 2 individuals who required 305 mg. per day and another 2 for which 103 mg. was sufficient. With respect to valine (Leverton *et al.*, 1956b) 15 young women were studied and the range of daily needs was from about 375 to 650 mg. For tryptophan (Leverton *et al.*, 1956c) 82 mg. per day was enough for 1 out of 8, 120 mg. was sufficient for 5 out of 8 and 157 mg. was sufficient for all. Phenylalanine (Leverton *et al.*, 1956d), in the presence of 900 mg. of tyrosine, was satisfactory for all 10 young women at the level of 220 mg. per day. At the 120 mg. per day level 1 out of the 10 young women

remained in nitrogen equilibrium. Data are less complete with respect to the range of phenylalanine needs in the absence of tyrosine. Three subjects appeared to need about 420 mg., whereas one needed more than 620 mg. In the case of leucine (Leverton *et al.*, 1956e) 620 mg. per day was considered satisfactory for all 8 individuals, but 170 mg. was satisfactory for 2 out of 8, while on 95 mg. per day all were in negative balance.

The lysine requirements of 14 young women have been studied by Jones *et al.* (1956). While 400 to 500 mg. per day appeared to be adequate for most of the subjects there was one (#8) who required at least 1600 mg. daily. The isoleucine requirements of 7 healthy young women were studied by Swendseid and Dunn (1956) with the following results: 3 needed 250 mg. daily, 3 needed 350 mg. and 1 needed 450 mg. isoleucine daily in order to maintain nitrogen equilibrium. The methionine requirements of 8 young women were studied by Swendseid *et al.* (1956) when cystine was also in the diet. Three individuals were in nitrogen equilibrium when 175 mg. of a mixture containing 75 mg. methionine was fed daily. At the other extreme 250 mg. (in the presence of 200 mg. of cystine) was required by 1 individual.

If we accept at their face value the results on young men and women from the different laboratories which have applied similar methods we come up with the ranges indicated in Table III.

TABLE III
RANGES OF DAILY REQUIREMENTS FOR MEN AND WOMEN

Amino acid	Low (mg./day)	High (mg./day)	High/Low
Tryptophan	82	250	3.0
Valine	375	800	2.1
Phenylalanine	420	1100	2.6
Lysine	400	1600	4.0
Methionine	175 ^a	1100	6.3
Threonine	103	500	4.9
Leucine	170	1100	6.5
Isoleucine	250	700	2.8

^a Only 65 mg. was methionine; the rest was cystine.

In view of the fact that these results were most often obtained by studying a total of not more than 30 individuals, and furthermore that the lowest levels of intake were not thoroughly investigated, it becomes apparent that variations in the general population must be large—far beyond what might be regarded as of academic interest. Placing the males and females in separate categories diminishes but does not solve the problem.

We are not here discussing the question of methodology or whether there is other evidence with respect to amino acid needs which is in conflict with that cited in this chapter. We are concerned only with individuality in needs and think it is only safe to assume, until evidence is available to the contrary, that every valid method for ascertaining individual needs at different ages, will, when applied, reveal about the same degree of individuality as that arrived at by the studies cited.

An important conclusion from the author's point of view is that it is unsafe to assume that any individual has about average amino acid needs. The chance that any randomly selected individual will be in the median third of the population with respect to the needs for one amino acid, is one in three. The chance that he will be in the median third with respect to 8 amino acids is about 1 in 6561. If the needs for the respective amino acids are not wholly independent, then this chance would be increased somewhat but not enough to alter one's basic thinking on the subject.

VI. DO INDIVIDUAL NEEDS DIFFER QUALITATIVELY?

There are many indirect evidences which indicate that some specific amino acids which have not been found to be essential nutritionally for adults, may nevertheless be needed by some individuals for maximum health. Since no direct attack on this problem has been made, it seems unwise to speculate at length.

Arginine has been borderline with respect to its nutritional essentiality for experimental animals. It is not commonly needed by adults for maintenance of nitrogen equilibrium. Albanese (1950a) listed it as "probably not required" by infants. All of this suggests, in the light of our earlier discussion of the gradation of states in which genes may exist, that some individuals may possess metabolic machinery which makes the production of arginine difficult. If this is the case, such individuals might benefit from arginine administration. Albanese (1950b) cites an example in which a very low sperm count in a 30-year-old individual was increased severalfold by the administration of 8 gm. of arginine. Since the arginine content of sperm cells is extraordinarily high, the finding seems a reasonable one.

The question of the beneficial effects of glutamic acid administration on mentally deficient children has been the subject of a great deal of discussion. That suggestive results (speaking conservatively) have been obtained, makes more probable the possibility that in some individuals the metabolic machinery for producing this amino acid has a limiting effect, from the functional viewpoint. The evidence is even stronger that glutamine production may be a limiting factor for maximum health

in certain individuals. Its efficacy in the treatment of ulcers (Shive *et al.*, 1957) and of alcoholism (Rogers and Pelton, 1957a) is strongly indicated and preliminary studies indicate that its administration enhances the test scores of mentally deficient children (Rogers and Pelton, 1957b). This is obviously a case where no all-or-none law applies. If there are some individuals who are markedly benefited by glutamine administration and others who are not affected at all, this is what one might expect on genetic grounds.

A general observation which is in line with the concept we are discussing, is that the so-called "nonessential amino acids" do not belong as strictly in this category as the first evidence indicated (Albanese, 1950c). On the basis of present evidence, the possibility exists that the list of amino acids, essential for maximum health, may not be identical for all individuals.

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