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Biochemical Individuality

THE BASIS FOR THE GENETOTROPHIC CONCEPT

UNIVERSITY OF TEXAS PRESS

Austin & London

Preface

THE WRITING of this book is based upon the need in human biology and medicine for more attention to variability and individuality at the physiological and biochemical levels. The potentialities arising from intensive study in this area are believed to be truly phenomenal because of the widespread existence of critical individual needs which can often be cared for if they are recognized.

Although ancients and moderns alike have called attention to variability and individuality as factors particularly related to disease susceptibility and moderns have recognized that variability is indispensable to evolution, comparatively little research time and effort have been devoted to definitive study in physiology and biochemistry as to precisely how so-called normal individuals differ from each other. Such study necessarily involves repeated observations on the same individuals, in contrast to a series of single observations on representative populations. No attempt to bring together the available biochemical material on normal variation has been previously made so far as I know.

Because of the diverse types of recorded observations which are pertinent to the subject and the fact that many of the observations have been made by those who have had little or no interest in individuality as such, it has not been possible to collect the material for this book in a highly systematic manner. If, for example, one looks up the word "variability" in various indices, virtually nothing is found. Because of the diverse

nature of the data it has not been possible to cover at all adequately the various topics on which some information may be available, and incompleteness must be taken for granted. My regret is that the thought, opinions, and data of many individuals, particularly physicians, who may be genuinely interested in the subject, have not been cited. This is partly because an interest in variations and individuality has often been considered a hobby and has not led to serious publications. This field of interest has not gained the respectability that it deserves.

My own particular interest in this subject probably stems from the laboratory observation, over twenty years ago, that, although creatine was described by Beilstein as a bitter biting substance, it was found to be absolutely tasteless to many. About the same time, I noted that some otherwise normal individuals were unable to detect skunk odor. I began to be convinced more than ten years ago that *differences* between human beings (as well as their similarities) needed to be brought to light, because they are crucially important factors which must be taken into account if many human problems are to be solved. The ideas which grew out of this concept were set forth in two books, *The Human Frontier* and *Free and Unequal*. When my interest in this area first developed, I regarded it as considerably divergent from my chosen field of research interest—biochemistry. However, as time has gone on and research results have accumulated, it has become clearer to me that individuality and applied biochemistry are inextricably intertwined. I no longer regard my interest in individuality as a departure from biochemistry.

Individuality in nutritional needs is the basis for the genetotrophic approach and for the belief that nutrition applied with due concern for individual genetic variations, which may be large, offers the solution to many baffling health problems. This certainly is close to the heart of applied biochemistry.

The point of view which has developed as a result of this study has important implications not only for biology and medicine, but also for anthropology, psychology, child development, education, and even religion, business, law, and politics. These implications are, of course, outside the scope of this volume.

Although I am convinced of the substantial truth of the general thesis of this book, I have endeavored to avoid dogmatism or the expression of my ideas with any degree of finality. Much of the evidence presented is far from being as satisfactory as it would have been had the investigations cited been interested in the problem of individuality Within a relatively few years, it is my hope that much better evidence will be forthcoming which will be the basis for the acceptance and probable modification of the point of view set forth in this volume. It is inevitable that there will be some mistakes and some questions of interpretations which can reasonably be raised. Serious students can be trusted, however, not to discard the basic thesis because they have doubts about a few items.

For the errors of omission and commission I take full responsibility, but I do wish to express my gratitude to my colleagues who have shown forbearance and to those who have given material assistance. The list of those who have contributed ideas, furnished material or citations, or have given substantial moral support includes the following:

Errett C. Albritton
Barry J. Anson
Ernest Beerstecher, Jr.
Helen K. Berry
Otto A. Bessey
Ludwig W. Blau
Oscar Bodansky
William Duane Brown
Helen B. Burch
Leland C. Clark
Konrad Dobriner
Harry J. Deuel, Jr.
L. C. Dunn
Vincent duVigneaud
Charles H. Eades, Jr.
Martin G. Ettlinger
Arthur L. Fox
Daniel H. Funkenstein
John W. Gowen
Alan Gregg
T. F. Gallagher
Arild E. Hansen
Harry Helson
Joel H. Hildebrand
Hudson Hoagland
Julia Outhouse Holmes
T. Duckett Jones
Ancel Keys
C. Glen King
Kenneth Hurley
Elwood H. LaBrosse
William K. Livingston
Pauline Beery Mack
Roy B. Mefferd
Herschel K. Mitchell
John P. Nafe
Richard B. Pelton
Gregory Pincus
Oscar Riddle
Lorene L. Rogers
William C. Rose
Frank W. Sayre
Robert W. Shideler
Howard T. Simpson
Robert P. Wagner
Alfred H. Washburn
Robert R. Williams
Lemuel D. Wright

This list does not include a number of students who have contributed citations in connection with their course work and to whom I am most grateful.

To Mrs. Katherine Neal and Mrs. Martha Ann Zivley I am much indebted for clerical and editing help.

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They conclude that "a single sampling every year would, generally speaking, be sufficient to classify a child regarding plasma alkaline phosphatase activity." The over-all range in the tabulated data for over 600 subjects was from 1.29 to 14.00 units. Although males and females different somewhat in the progressive changes with age and the largest ranges were observed for the period 10-14 years, large ranges appeared both in boys and girls.

A number of other investigations corroborate the fact that alkaline phosphatase values exhibit wide variance from individual to individual.[2,3,4] In certain pathological conditions—Paget's disease, hyperparathyroidism, and obstructive jaundice—the values may rise to 10 or 50 times the average normal value.[5] In normal individuals the levels of alkaline phosphatase are not affected significantly by an 18-hour fast, a high protein meal, or a 40-hour period of very high fat intake.[6] In rickets the values are high and subside slowly but definitely when the condition is treated nutritionally.

We shall not go into the question of the existence of different alkaline phosphatases in the blood or their origin. From the standpoint of our discussion the conclusion is clear: Wide inter-individual differences exist with respect to this type of enzyme as it appears in the blood. On the basis of observations cited above, it is apparent that these inter-individual differences are significant in relation to metabolism and disease.

Acid Phosphatase of Blood

In one investigation Gutman and Gutman[3] found the range of acid phosphatase in 10 normal adults to be from 0.6 to 2.0 units. In certain diseased conditions the values were high, up to 5.0 in an advanced case of Paget's disease. The substrate used was monophenyl phosphate.

Using adenosine phosphate as the substrate at *p*H 4.8, Meister[6] found for 24 individuals a range of 0.20 to 0.66 units. These units, of course, are not the same as those in the previous citation.

In a third investigation, in which sodium-β-glycerophosphate was used as the substrate, Tuba, *et al.*,[3] have found both the spring and fall acid phosphatase values for adults to vary through the same range, 0.0 to 1.2 units. For children, boys and girls alike, the range was 0.0 to 1.6 units. No attention was paid to inter-individual differences.

Acid phosphatase is widely distributed in tissues. Male prostate glands[7] are extraordinarily rich, and this enzyme is implicated in the physiology of sex. Men excrete in the urine about 3.5 times as much acid phosphatase as women.[8] The prostate glands of individual well men vary in acid phosphatase content per unit weight through at least a 4-fold range.

Blood Arginase

The amount of arginase in blood has been studied in enough different individuals and with enough samples to demonstrate that activity of this enzyme in erythrocytes varies widely from individual to individual, but is, to quote Clark and Beck, "remarkably constant for a given individual."[9] The range found in a group of about 200 normal children was from 2.0 to 8.4 units per 100 ml. of blood. When a group of 81 children were tested twice on consecutive years, the one who had the lowest value (2.5) the first year exhibited the lowest value the second year (2.0). The individual child who exhibited the highest value the second year (7.6) also showed a correspondingly high value (7.1) the first year. There were individual children who showed substantial variation, the maximum being that of a child who exhibited a value of 3.0 one year and 6.5 the next, but most children did not vary more than a half unit.

In the case of this enzyme there is a highly significant, though not large, sex difference (of the order of 10 to 20 per cent) which appears even before pubescence. Females tend to have higher arginase values. Adult values are substantially like those for children. There is no significant change during pregnancy. We have found no reports indicating that elderly people have been studied specifically in this connection.

Cholinesterase in Blood

Sawitsky, *et al.*,[10] have shown that the cholinesterase activity of corpuscles in 15 normal individuals varied through a range of 7.25 to 10.34 units per ml. and of the plasma from 1.5 to 5.0 units per ml., but that for a given individual the values were relatively constant. The relative constancy of intra-individual values and the variation between individuals have been confirmed by other investigators.[11] Females show more variation than males, but otherwise there is no significant sex difference. Age appears not to be an important factor. A logical assumption is that the variation is a reflection of genetic differences.

Hall and Lucas[12] found a variation of 2.7 to 7.24 units of cholinesterase in the blood serum of 25 normal human individuals. Variations between different samples from the same individual were small.[13] They also found similar inter-individual differences in other species—horses, dogs, guinea pigs, cats, rabbits, and chickens. Interspecies differences were apparent as well; the range for cats, for example, was from 1.84 to 2.80 units, whereas for rabbits it was 0.35 to 0.70 units. More recently Mann, *et al.*,[14] found more than a 3-fold range in cholinesterase in the serum of normal humans and practically a 10-fold range when patients with

hepatic cirrhosis were included. In viral hepatitis the cholinesterase decreases with the onset and increases with convalescence. De la Huerga, *et al.*,[15] using a colormetric method, found an inter-individual range of 130.0 to 310.0 micromoles per 1 ml. per hour for 132 normal individuals. Serial determinations in 20 normal persons over a period of 1 month did not show any significant variation in serum cholinesterase activity.

The sum total of the observations is in line with the supposition that genetic factors are highly important in determining the activity of this enzyme in the bloods of different individuals and that the level has physiological significance.

Serum Amylase

The activity of this enzyme was found to vary in "healthy normal" subjects from 40 to 179 units per 100 ml. of serum.[16] In "normal" hospitalized patients the variation was from 10 to 500 units per 100 ml. Regarding the constancy in a given individual, Somogyi says that "if the normal level for a given person is known, even moderate changes are significant, for the diastase content of the blood in any healthy person is maintained at a fairly constant level."

Among medical technologists the normal limits, using an iodometric method, are considered to be from 0 to 320 units. In a series of 23 individuals the range was from less than 80 up to 1070. Five of these individuals were judged to be abnormal, and one was considered borderline. Two cases of acute pancreatitis yielded values on admission of 1600 and 3200 units, respectively.[17]

The level of this enzyme is practically unchanged from childhood to adulthood; there are apparently no sex differences, and the level is not affected by the amount or type of food, by fasting, diuresis, dehydration, exercise, or sleep. This enzyme, therefore, constitutes another example in which variations between individuals are large (up to 50-fold including a hospital population), but those exhibited by a single individual are small. Since high serum amylase levels appear to be associated with pancreatic impairment,[18] there is ample reason to suppose that differences have a functional significance.

Plasma Catalase

Study of plasma catalase activity on an individual basis has been limited in scope. For 50 adults the range was found to be from 4.2 to 9.5 per ml. of plasma.[19] One of the normal individuals was studied for five days, and the following values were obtained: 9.5, 8.5, 9.5, 7.0, 9.5. Further study is required before one could conclude definitely that there are significant inter-individual differences. The available evidence points

in that direction. In various anemias the values may be 50 or more. In one "diagnostic problem case" the value was 42. It seems highly probable that "normal" differences have physiological significance.

Serum Phenolsulfatase

The activity of this enzyme in the serums of 24 different individuals[20] varied from 0.3 to 15.5 units per ml. No study has been made of the constancy of the value for specific individuals. The wide range noted above is accompanied by a correspondingly wide range in excretion values: 0.9 to 19.7 units per ml. of urine.

Serum Lipase

The range of values for this enzyme corresponds to 0.0 to 1.5 ml. $N/20$ sodium hydroxide required to neutralize the fat acids released by 1 ml. of serum under controlled conditions.[18] Since 0.05 ml. of $N/20$ sodium hydroxide solution should be easily detectable, this corresponds to at least a 30-fold range and is in line with the large range in the blood lipids which is known to be inter-individual (p. 54). Because of lack of interest in the question apparently no investigation has been made regarding the constancy or lack of constancy of the lipases in the blood of specific individuals.

Peptidases of Human Erythrocytes

Using four different peptides as substrates, Adams, *et al.*,[21] found for 10 normal individuals the following ranges in activity (proteolytic coefficient $\times 10^4$).

Substrate	Range
Glycyl-L-proline	13–23
L-Leucinamide	2–12
Glycylglycine	2–12
Triglycine	6–19

These ranges, which average over 4-fold, have not been investigated for intra-individual constancy.

Aldolase in Blood

The aldolase activity of human serum has been investigated and found to range slightly over 2-fold in 68 normals and up to 10-fold if diseased individuals are included.[22] No special attention has been paid to the constancy of the values for specific individuals. The tissues of laboratory rats show on the average a little less than a 2-fold variation from animal to animal.

within the "normal" range, this randomness was not universal. One individual, for example, showed consistently a low blood sugar; every one of six determinations yielded values below a commonly accepted normal range. Another individual had high blood uric acid; every value was above the accepted range. A third individual exhibited serum amylase values below the accepted "normal" range. A fourth individual exhibited high alkaline phosphatase values; every one was above the accepted normal range. A fifth individual exhibited high acetylcholinesterase values, every one of which was well above the accepted normal range.

Not only did individuals exhibit high or low blood values, but other distinctive characteristics also appeared in the individual data. One individual, for example, showed a 2-fold spread in his blood creatinine values, with general lack of agreement between values. In contrast, the majority of the individuals showed high consistency with respect to blood creatinine values; one individual yielded *identical* values in six determinations. One individual showed relatively high blood values for sugar, creatinine, urea, uric acid, and lactic acid and no low values for any of the items studied. Another individual showed relatively low blood values for acetylcholinesterase, sugar, phosphorus, lipase, and acid phosphatase but a relatively high value for urea.

Among the distinctive differences observed in the mineral analysis study were: (1) nearly a 6-fold difference between two individuals (no overlapping in values) in urinary calcium excretion, (2) nearly a 3-fold variation in plasma magnesium, (3) over a 30 per cent difference (no overlapping of values) in the sodium content of blood cells, (4) a 4-fold variation (with no overlapping values in 21 to 25 samples, respectively) in salivary sodium, (5) a 5-fold variation in salivary magnesium with no overlapping values in 7 to 15 samples, (6) taste threshold values that often differed consistently from individual to individual over a 20-fold range.

It was noted that not only were certain blood values above or below the "normal" range for specific individuals but also that, regardless of the positions in the ranges, each individual exhibited a distinctive pattern. Abundant evidence was obtained from these two studies alone to suggest the importance of studying biochemical individuality and its relationship to susceptibility to a host of diseases. The distinctiveness of these studies lies in the fact that repeated samples from the same well individuals, collected under basal conditions, were analyzed for many different constituents. This procedure is not often followed.

The whole problem of human health and welfare is vastly different if the population, instead of being composed mostly of individuals with

normal attributes, is made up of individuals all of whom possess unusual attributes—individuals who deviate from the normal range in several of the numerous possible particulars.

To make the pertinence of our hypothesis even clearer, let us consider the import of this idea in connection with a hypothetical situation. Let us assume the existence of a population of ten men (Group I) all of whom have about average height, about the same average foot size, about the average amount of hair on their heads, about the average tendency to put on body fat, about the average tendency to consume alcoholic liquors, about average sex urge, about the average type of lenses in their eyes (neither farsighted nor nearsighted), about average emotional reactions, about average digestive tracts, and about average teeth.

Contrast this group with another hypothetical population of ten men (Group II). The men in this second group may yield similar average values and be average or near average in many respects. One, however, is six feet six inches tall, one has long and very narrow feet, one is highly rotund and finds it very difficult to reduce, one is completely bald, one is an alcoholic, one has an extreme sex urge, one is nearsighted, one is subject to fits of anger and depression, one suffers from digestive upsets, and one has very bad teeth.

In the population represented by Group I the problem of finding a hotel bed long enough to sleep in doesn't exist; the problem of finding shoes that fit is negligible; dental problems are not serious; the problem of mental health may be absent; the problems of obesity, baldness, alcoholism, sex aberrations, nearsightedness, farsightedness, and indigestion are all practically nonexistent. Within Group II, however, *all* of these problems exist in acute form.

Both of these two imaginary populations of ten are possibly illustrative caricatures as compared with any real population, but we wish to call attention to the fact that Group II (each member of which is a deviate) may be much more like a real population than is Group I, consisting of individuals none of whom possess any marked deviations. It seems highly probable, or at least well worth considering as a possibility, that a host of human problems, medical and nonmedical, exist because real populations resemble Group II more than they do Group I. If we consider populations to be like Group I, we dodge (and fail to solve) this host of problems. If Group II approaches, in principle, a typical population, the inescapable problems cannot be solved until we become conversant with the nature, magnitude, and distribution of the underlying deviations.

Biochemical individuality thus becomes basic to the solution of those problems in which ***biochemical*** deviations come into play. How num-

Table 7. Some Ranges in Concentrations of Miscellaneous Organic Constituents of Normal Human Blood[a]

Constituent	Source	Range, mg. per cent	
Glucose	Whole blood	84	125[b]
		60	160[c]
		(40	160)[c]
Glycogen	Whole blood	1.2	16.2
Ribonucleic acid	Plasma	3.9	5.9
Desoxyribonucleic acid	Plasma	0	1.6
Adenosine triphosphate	Whole blood	31	57
Pyridine nucleotides	Whole blood	2.6	4.6
Lactic acid	Whole blood	0	41.0
Pyruvic acid	Plasma	0.4	2.0
α-ketonic acids	Whole blood	0.0	3.1
Citric acid	Serum	1.6	3.2
Malic acid	Plasma	0.1	0.9
Glucuronic acid	Serum	1.6	3.6[d]
	Whole blood	2.5	8.5[d]
Creatine	Plasma	0.0	0.8
Creatinine	Whole blood	1.0	2.0
Glutamine	Plasma	5.0	12.0
Urea	Whole blood	11	48[c]
Uric acid	Plasma	2.0	5.6
	Corpuscles	0.8	3.0
Acetylcholine	Plasma	0.30	4.8 μg[f]
Histamine	Whole blood	0.02	0.08[g]
Ergothioneine	Whole blood	1.9	5.5
Neutral fat	Corpuscles	11	148
	Plasma	24	260
Phospholipid	Plasma	110	220
Total lipid carbon	Plasma	218	1780[h]
Total lipid phosphorus	Plasma	(0.7) 1.8	16.6[h]
Total lipid nitrogen	Plasma	(1.7) 4.0	23.9[h]
Lipid amino nitrogen	Plasma	(0.2) 0.5	8.2[h]
Total cholesterol	Plasma	109	428[h]
	Plasma	116[h]	700[i]
Lecithin	Serum	50	204
Cephalin	Whole blood	31	118
	Plasma	0	29[j]

[a] Unless otherwise indicated, data are from Errett C. Albritton, *Standard Values in Blood*, W. B. Saunders Company, Philadelphia, Pa., and London, Eng., 1952, pp. 89–92, 101.

[b] Clark W. Heath, *et al.*, *What People Are*, Harvard University Press, Cambridge, Mass., 1946, p. 124.

[c] F. William Sunderman and F. Boerner, *Normal Values in Clinical Medicine*, W. B. Saunders Company, Philadelphia, 1949, pp. 112, 111.

than a 4-fold range in content, is worthy of especial note since highly pertinent data with respect to the more specific measurement, the "serum protein-bound iodine," are available. From one study[19] of a group of 402 men 18 to 56 years of age, the spread in the protein-bound iodine was calculated for 99 per cent of the (normal) population to be 3.32 to 9.82 μg. per 100 ml. The actual spread in the 402 men appeared to be 2.5 to 11.5 μg. per cent. In another study[20] in which the "normal range" was concluded to be about the same as in the paper cited above, the actual range, including patients with various pathologies, was from 0 to 48.2 μg. per cent. One individual, not classed as hypothyroid, exhibited a value as low as 0.6 μg. per cent. In a third study[21] the range found in 47 plasma samples was from 1.1 to 28 μg. per cent. It is highly significant from the standpoint of our discussion that in these studies and others[22] the protein-bound iodine values are found to be relatively constant for any given healthy subject over a considerable period of time. In this case we have strong evidence of individuality and a wide spread in values.

The case of copper is also worthy of special note because several investigations have indicated that while inter-individual variations in plasma copper may be about 2.4-fold, the intra-individual variations (particularly in males) from day to day and week to week are relatively small.[23] Little attention has been paid to the specific problem of inter-individual differences in this connection.

Miscellaneous Organic Constituents of the Blood

Various organic constituents of blood have been found in normal individuals in the ranges of concentration shown in Table 7.[16,24–32] There are many items in the list for which there is a 3- or 4-fold variation, and about a dozen for which the variation is of the order of 10-fold or more. These data strongly suggest that marked inter-individual differences exist,

[d] Abraham Saltzman, Wendell T. Caraway, and Irving A. Beck, *Metabolism, Clinical and Experimental*, 3, 13 (1954).

[e] W. G. Fishman, M. Smith, D. B. Thompson, C. D. Bonner, S. C. Kasdon, and F. Homburger, *J. Clin. Invest.*, 30, 685 (1951).

[f] Harold H. Scudamore, Louis J. Vorhaus, II, and Robert M. Kark, *J. Lab. Clin. Med.*, 37, 862 (1951).

[g] E. Haworth and A. D. Macdonald, *J. Hygiene*, 37, 237–238 (1937).

[h] Irvine H. Page, Esben Kirk, William H. Lewis, Jr., William R. Thompson, and Donald Van Slyke, *J. Biol. Chem.*, 111, 616–618 (1935).

[i] Maurice T. Fliegelman, Charles F. Wilkinson, Jr., and Eugene A. Hand, *Arch. Dermatol. Syphilol.*, 58, 414–417 (1953).

[j] V. Posborg Petersen, *Scand. J. Clin. Lab. Invest.*, 2, 45 (1950).

[k] Schoenheimer-Sperry method.

but they do not offer proof except where repeated samples have been analyzed from the same individuals.

The glucose values are worthy of attention because of the large number of determinations that have been made in many laboratories. There is evidence of substantial intra-individual variation in glucose values which is in part responsible for the range of the observed values.[33,34] In spite of this normal variance in values in the same individual, however, there is evidence that inter-individual differences exist among well people. Some, on repeated tests, tend to have low values, some intermediate, and some high.

The acetylcholine values show an unusually wide spread. Although no specific study has apparently been made to ascertain the magnitude of intra-individual differences, relative constancy of values in the same individual seems to be taken for granted, and the range of values is reported to be at a higher level for those suffering from bronchial asthma.[28]

The histamine values of normal individuals have been found to vary about 8-fold (1 to 8 μg. per cent), but repeated tests on the same persons indicated that an individual's values do not vary to a marked degree.[29] The histamine content of the blood in leukemias[35,36] varies from 2.1 to 706.2 μg. per cent, and some investigators have been concerned about deciding when an individual is normal. In case a supposedly normal individual shows a highly unusual value, there is a temptation to discard his value and if necessary find something wrong with him which might justify such an exclusion. It is interesting that there are very wide interspecies differences in histamine blood levels.[37,38] The evidence indicates that each individual probably tends to maintain a characteristic level of histamine in his blood. This does not, of course, mean that the value is static or is uninfluenced by environmental factors.

In the case of the blood lipids the evidence that many of the variations are inter-individual is convincing. Man and Gildea,[39] in studying the variation in blood lipids in normal subjects (in the postabsorptive and well state), collected repeated samples from the same individuals over a period of 3 months to 4 years. The four men and six women studied tended to have characteristic levels. One of the four men had consistently the lowest minimum and lowest maximum values for cholesterol, lipoid phosphorus, and titrated fatty acids. Another of the four had the highest values of the group. One of the six women (M.G.) had the lowest minimum and the lowest maximum among the women in practically every case. Sperry[40] concluded, in his study of the blood cholesterol values, that "the range of variation in a given person over considerable periods of time is far less than the variation among different persons."

Page, *et al.*,[41] found that "variations of age, from 20 to 90 years, have not been found to have a determinable influence on either the amount or the composition of the plasma lipids." From this work, it is clear that, although there is some tendency for the various lipid values to be correlated with each other, this is by no means always the case. Patterns are exhibited, so that an individual may exhibit a high value for one lipid constituent and a relatively low one for another. These, too, are doubtless influenced by environmental factors, particularly nutrition. We shall refer to this study in a later paragraph.

Table 8. Ranges in Amino Acids in Blood Plasma

	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

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

Amino Acids in Blood

In a recent quantitative microbiological study of the amino acids in the plasma of 17 young fasting males,[42] the wide ranges shown in Table 8 were observed. The ranges for ten of these amino acids average about 4-fold or more. Since the above study and similar ones preceding it[43,44] often involved the analysis of a single sample from each individual, one cannot conclude that significant inter-individual differences exist. One might be inclined to regard these observed differences as due to chance intra-individual fluctuations were it not for the fact that we find in urine