Biochemical Individuality

The Basis for the Genetotrophic Concept

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Foreword

TRADITIONALLY the role of the biochemist has often been to remind the clinician of biochemical laws as well as discover them, to accent the uniformities as well as find them. Dr. Williams' refreshing message in this book accentuates the meaning and significance of the exceptional, the peculiar, the individuality of the individual. In this book he champions biochemical variety. As a biochemist, expert in metabolism, by what he calls the genetotrophic approach, he provides us with a way of reconciling the unusual and so-called abnormal bodily chemical processes with the "normal." This he does by being mindful of the almost infinite variety of interplaying genetic factors. Hereditary factors have been shown in morphology and in disease susceptibility. Dr. Williams carries a comparable set of interpretations into the observations of the body's myriad metabolic processes.

It behooves students of human biology to examine with as much imagination as rigor the kinds of thinking we apply to our observations of living tissue. Especially in clinical work we need to be chary of assuming uniformly sufficient single causation or cause for events. We need to remember not merely the environment, but also the individual make-up of what the environment surrounds. For every organism brings its own environment from the past—its heredity.

And, if a biochemist elects to insist on these things, what voice could be more fresh and strong? The new insights which are developed in this book should be explored by every student of medicine.

ALAN GREGG, M.D.

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 in-

evitable 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:

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ROGER J. WILLIAMS

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I

Biochemical Variation: Its Significance in Biology and Medicine

SINCE the days of Darwin, it has been generally recognized by biologists that variability in organisms is a *sine qua non* of evolution. Variability has been subjected to extensive mathematical study and is a basic concept with which the vast field of statistics is concerned. Biologists have not been unappreciative of the fact that intraspecies variability may be great. Julian Huxley[1] has pointed out that the variability in the human species is of much greater magnitude than that in animals, because men have much greater migratory propensities and are more neglectful of large differences in color and appearance when choosing mates. Among his illustrations of divergence he says that the "difference between the mind of, say, a distinguished general or engineer of extrovert type and an introvert genius in mathematics or religious mysticism is no less than that between an insect and a vertebrate."

Hippocrates spoke of man as "that infinitely variable organism without which human disease is impossible," and Gray[2] has suggested that Hippocraties' ideas translated into modern terms may be stated: "it takes two to make a case of illness; he who gets sick and the bug that bites him." Galen, the Greek physician, about 600 years after Hippocrates, voiced the same general thought when speaking of disease; he said, "No cause

can be efficient without an aptitude of the body." Coming to more modern times, Sir William Osler quoted with approval the statement of the older physician, Parry of Bath, to the effect that it is "more important to know what sort of patient has a disease, than to know what sort of disease a patient has." One of the most modern exponents of the same idea was George Draper, who founded the Constitutional Clinic of the College of Physicians and Surgeons, Columbia University, in 1916, and who with his collaborators published a book, *Human Constitution in Clinical Medicine*, in 1944.[3]

The subject of *variation* with which we are predominantly concerned is, therefore, an old one, and it might be supposed that there would be little new to say. It is our opinion, however, based upon the data presented in this volume, that variability is vastly more important in the biological sciences and in medicine than it is currently assumed to be. And, because of what a study of variability in nutritional needs can do for medicine, such study deserves ten times more direct attention in terms of research time and effort than it is now receiving. The reader must be left to judge for himself whether these opinions are based upon a reasonable interpretation of the facts.

A commonly accepted point of view in the field of biology and related disciplines—physiology, biochemistry, psychology—and in the applied fields of medicine, psychiatry, and social relations appears to be that humanity can be divided into two groups: (1) the vast majority possess attributes which are within the normal range; (2) a small minority possess attributes far enough out of line so that they should be considered deviates. This point of view is more often tacitly assumed than expressed and is illustrated by the fact that when an obstetrician can inform a mother that her newborn child is "normal in every way," everyone is happy; but if the infant must be pronounced abnormal, everyone concerned is distressed.

The most commonly accepted line of demarcation between normal and abnormal in biological work is the 95 per cent level.[4,5] That is, all values lying outside those possessed by 95 per cent of the population may be regarded as deviant values, and any individual who possesses such deviant values may be regarded as a deviate.

If we consider the possibility that among the numerous measurable attributes that human beings possess there may be many which are not mathematically correlated, we are confronted with an idea which is opposed to the basic dichotomy of normal and abnormal mentioned above. If 0.95 of the population is normal with respect to one measurable item, only 0.902 (0.95^2) would be normal with respect to two measurable items

and 0.60 (0.95^{10}) and 0.0059 (0.95^{100}), respectively, would be normal with regard to 10 and 100 uncorrelated items.

The existence in every human being of a vast array of attributes which are potentially measurable (whether by present methods or not), and probably often uncorrelated mathematically, makes quite tenable the hypothesis that *practically every human being is a deviate in some respects.* Some deviations are, of course, more marked and some more important than others. If this hypothesis is valid, newborn children cannot validly be considered as belonging in either one of two groups, normal and abnormal. Substantially all of them are in a sense "abnormal." In the majority, the "abnormalities" may be well enough concealed so that they are not revealed by clinical examination, though they may easily have an important bearing upon the susceptibility of the individual child to disease later in life.

Though this hypothesis may appear perfectly plausible, it has not been tested by experiment so far as we have been able to ascertain. Individual human beings have never been measured in enough different ways in which norms are established so that the data are conclusive.

The question of the validity of this hypothesis is not an academic one. As will be made clear in the later pages of this volume, there is a strong probability that the postulated deviations existing in almost everyone are closely related to the fact that practically every individual born into this world sooner or later gets into distinctive health difficulties of one kind or another. And the number of kinds of such difficulties, like the number of possible deviations, is legion.

To make this discussion more concrete, let us consider briefly some studies on groups of "normal" young men made in our laboratories which tend to support the hypothesis outlined above.[6] In one study five samples (sometimes six) of blood were drawn from each of eleven individuals at weekly intervals under basal conditions; by the use of conventional clinical methods, the samples were carefully analyzed for sugar, lactic acid, urea, creatinine, uric acid, inorganic phosphorus, amylase, lipase, acid phosphatase, alkaline phosphatase, and acetylcholinesterase. In another related investigation a similar group of nine normal young men (eight of whom were individuals included in the other study) was studied by analyzing repeated samples of blood plasma, blood cells, urine, and saliva, for calcium, magnesium, sodium, and potassium and by repeated tests on the same individuals of their taste thresholds for the chlorides of calcium, magnesium, sodium, and potassium.

Although for certain items applicable to certain individuals the quantitative values obtained appeared to be a random assortment of values

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-

erous these problems are and how pertinent the deviations are will be more evident as the various areas of biochemistry are considered.

Certainly, one of the drives which has impelled many workers in the biological and related sciences to neglect, comparatively, the deviations which we consider as possibly crucially important is the desire to make generalizations. Without generalizations and laws science cannot exist. From the standpoint of developing a science of biology, it seems extremely desirable to formulate valid generalizations that will encompass all humanity, all mammals, or all members of any biological group. Actually, in the human-centered sciences directly related to medicine, there appears to be a strong tendency to focus attention on "normal man," a being about whom generalizations can be made. Almost any treatise which one may find dealing with the subjects of physiology, biochemistry, pharmacology, or physiological psychology is concerned almost wholly with normal man and his reactions. The subject of the significance of variation is most often neglected entirely, and it would appear not to be regarded as important.

We are of the opinion, however, that the hypothesis—every one a deviate—is potentially important enough for the understanding of susceptibility to disease that extensive data not now available need to be collected to test its validity and to open the way to more effective therapy and prophylaxis. The open door which presents itself when every individual is considered to be a potential deviate with respect to his nutritional needs will be discussed in Chapter XI, after the basis for this individuality in nutritional needs has been adequately explored.

The development of the area of biochemical individuality is made urgent by the foregoing considerations. It is made possible because of the introduction of new techniques and tools. Many of the facts related to biochemical individuality which are presented in later chapters of this book could not have been brought to light if it were not for some of the newer tools: chromatography, isotopic techniques, and physical methods of analysis and separation. The collection of data in the area of individuality is in its infancy, and newer techniques will make possible the collection of vastly more pertinent and satisfactory information than is available at present. Many of the data which are now available have been collected by investigators who appear to have no particular interest in variation as such or concern with its possible significance.

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II

Genetic Basis of Biochemical Individuality

All geneticists are agreed that what is inherited by organisms from their forebears is a range of capacities to respond to a range of environments. The characteristics that an organism possesses are fundamentally the outcome of the interaction of heredity and environment. If we state that characteristics are inherited, we make a false implication that environment had nothing to do with their production. This is never the case.

There are numerous characteristics, however, including many morphological features, in which under ordinary circumstances heredity plays the important role. The essential determinants for the duplication of the morphology of an oak tree, a rabbit, or an elephant are resident in the respective fertilized egg cells from which these organisms spring. Environment, as ordinarily encountered by these developing organisms, makes development possible and may, to a degree, modify the course of development, but the basic morphology is determined by the carriers of inheritance.

Not only are morphological species-differences transmitted through inheritance, but morphological characteristics which are peculiar to an individual organism are transmitted to its offspring in a similar manner.

It is well known, for example, that because of their postulated identical inheritance, the facial features of identical twins are often indistinguishable. It may be presumed that the morphological features of all the internal organs, which also show a high degree of variance (p. 18), are likewise inherited in the same sense. There is substantial evidence on this point to be cited later.

Although it is theoretically possible for environments to be altered artificially or otherwise so that morphological features will be substantially changed, the color of one's eyes, the relative size of one's feet, the curliness of one's hair, the patterns of one's fingerprints, and a host of other morphological features are primarily, under ordinary living conditions, the result of inheritance. Once the egg is fertilized, the living conditions in a healthy uterus established, and good food furnished the mother many morphological features are substantially determined. Even here, however, we must not forget the interplay of environment, because nutritional lacks or the effects of foreign chemicals may cause the production of even gross abnormalities in growing embryos.

It has also long been recognized that gross metabolic differences between organisms of different species are genetically determined. In birds the principal end product of nitrogen metabolism is uric acid; in mammals it is urea. In most dogs the end product of purine metabolism is allantoin (in Dalmatians uric acid constitutes an important part); in humans, uric acid is the corresponding principal end product. Inheritance is the determining factor here, as is true also for the differences with respect to ascorbic acid synthesis in rats, guinea pigs, and humans. Rats inherit the ability to synthesize ascorbic acid; neither guinea pigs nor humans inherit mechanisms for doing this, and hence these species are dependent on a dietary source of this vitamin.

As the subject of biochemical genetics has developed, it has become clear that inheritance and mutations govern not only the *gross* metabolic differences between different species but also intraspecies differences of a lesser magnitude.

Much of the earlier development in this area came about through the study of induced mutations in *Neurospora,* but the general principles clearly are applicable to organisms high in the biological kingdom. There is, on the part of those familiar with the field, not the slightest doubt that inheritance and the concurrent mutations govern the minute details of intricate chemical processes which take place in any organism. The finding in *Neurospora* of the ornithine cycle, for example, is one of many observations which tie together the whole biological kingdom and make more certain the universal application of the principles of biochemical genetics. Obviously the availability of suitable substrates (ulti-