of the i orbitals, it is to be expected that they would not make any important contribution to the hybrid bond orbitals.

The general qualitative agreement with experiment provides support for the theory that the potential barriers to internal rotation result from the interaction of adjacent hybrid bond orbitals with a small amount of f character. The magnitude of the potential barriers, about 4 per cent of the energy of the axial bond in case that there are three interacting bonds on each of the two atoms and proportionately less for a smaller number of bonds, is also reasonable. A detailed quantum-mechanical treatment of restricted rotation carried out along the lines sketched here should yield results that would permit a detailed test of the theory to be made; in the meantime I believe that the above simple treatment and the extensive empirical support of the theory provide justification for it.

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*IDENTIFICATION OF BLOOD CHARACTERISTICS COMMON TO ALCOHOLIC MALES**

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In 1947 our laboratory began the intensive study of alcoholism, on the presumption that individual differences in metabolism are basic to the etiology of the disease and that "no psychological stresses can make an individual an alcoholic unless he has inherited a metabolic pattern which renders him susceptible."[1] This working hypothesis—so designated at the time—has held our constant interest.

The difficulties of testing this hypothesis have been great, mainly because at the start almost complete ignorance existed as to how one individual might differ from another metabolically. Very few investigators have had any specific interest in gathering this type of information. Recently the senior author has attempted to assemble in a book entitled *Biochemical Individuality*[2] the available material on the

subject, most of it derived, however, from the work of those who had no interest in individuality as such.

At the time we embarked upon the study of alcoholism we had in mind the possibility of finding metabolic earmarks that might characterize alcoholics, and we indicated: "If the potential addict could be forewarned, avoidance of alcoholism would be made relatively easy."[1] This statement was made before we had developed the genetotrophic concept,[3] which emphasizes the potentialities of completely adequate nutrition for the prevention of the disease.[4]

The present discussion has to do with the progress we have made in finding metabolic earmarks which might be useful in detecting alcoholism-prone individuals before they become addicts.

Recently we have completed an experimental study of 53 male alcoholics, twenty-seven to sixty-two years of age, and 41 male control individuals, twenty-one to forty-eight years of age, who, although they consume some liquor, have avoided exhibiting alcoholic tendencies. The alcoholic subjects were studied in co-operation with the Austin State Hospital. Two preliminary studies[5, 6] had been very helpful in directing attention to items which gave promise of being significant in this connection. Two samples of venous blood were drawn on separate days under basal conditions from each of the 94 individuals. Cell counts and analyses were made on each sample. The results from the two samples were averaged and used in the computations.

The items listed in Table 1 were found to be significantly different for the controls and the alcoholics. Serum magnesium was higher in the alcoholic group, but the *P*-value was only 0.10. Figures 1 and 2 show the distribution of the values for two items in the list: serum potassium, which showed the most consistent differences, and the blood sugar levels, which showed the least consistent differences among the seven items.

TABLE 1

BLOOD VALUES FOUND TO BE DIFFERENT FOR CONTROLS AND ALCOHOLICS

	"Normal" Range (Albritton)	Control Average	Alcoholic Average	*P*-Value
Total leukocytes.....	3,480–14,840/mm³	6,450	8,420	0.001
Lymphocytes.....	1,000–4,800/mm³	1,520	2,020	0.001
Eosinophils.....	50–700/mm³	156	355	0.001
Blood sugar.....	76–96 mg/100 ml	96	106	0.01
Serum sodium.....	132–144 meq/1000 ml	134	141	0.001
Serum potassium....	3.6–4.8 meq/1000 ml	3.8	4.95	0.001
Serum calcium.....	4.0–5.5 meq/1000 ml	4.67	5.18	0.001

Urine samples were collected from the same 94 individuals at four regular times on each of two separate days. Equal volumes of these specimens were pooled, and the two composite samples from each individual were analyzed for a series of items. The results from the two pooled samples were averaged and used in the computations. It was not feasible under our conditions of operation to obtain 24-hour urine samples from these large groups.

A notable difference between the alcoholics and the controls was the level of creatinine in the urine on a volume basis. The alcoholic average was a little less than half that of the controls, and there was only one alcoholic in the whole group who exhibited a creatinine level higher than the mean of the control group. A

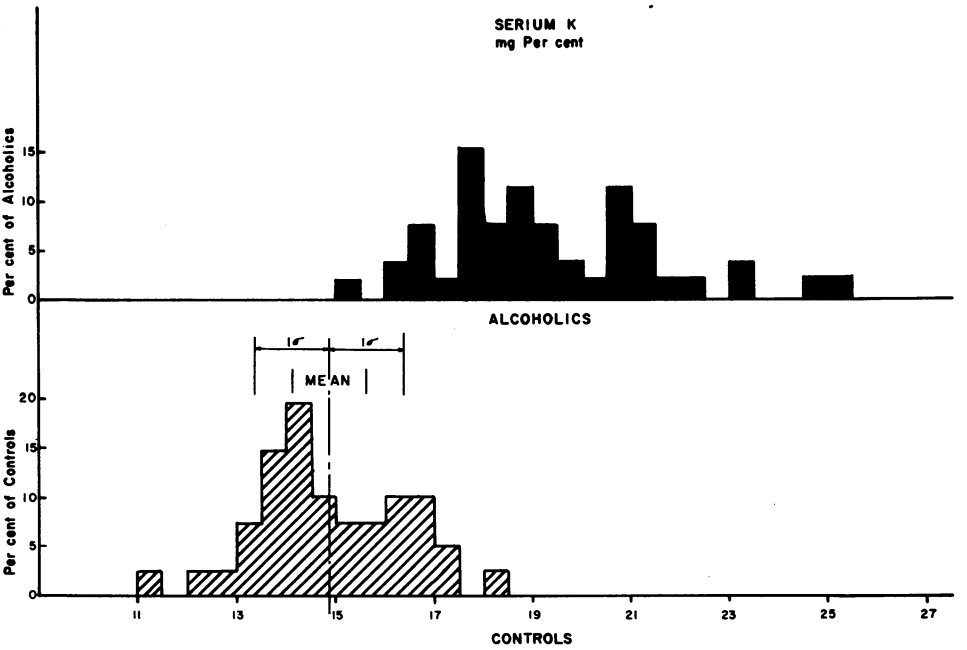

FIG. 1.—Serum potassium. Percentage distribution (to the nearest 0.5 mg per cent)

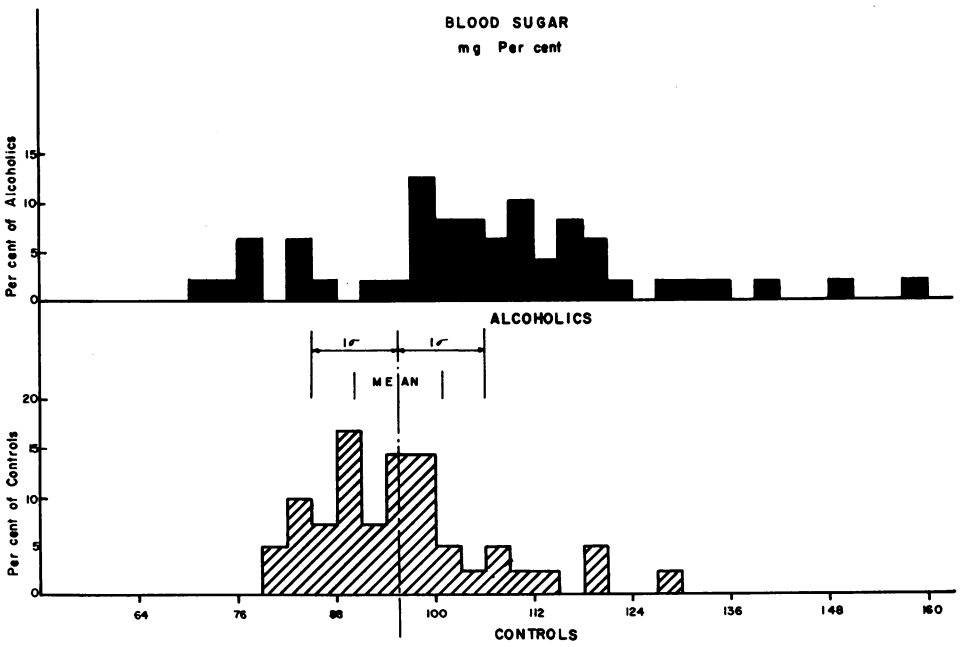

FIG. 2.—Blood sugar. Percentage distribution (to the nearest 3 mg per cent)

separate study in which three consecutive 24-hour samples from a smaller group of alcoholics were analyzed indicated that their daily creatinine excretion is about normal and that the lower creatinine level in alcoholics is due primarily to their urine being more dilute.

The urinary items which appeared significantly different for the two groups are given in Table 2. Urinary pH was measured but not found to be significantly different for the two groups.

TABLE 2

SIGNIFICANT URINARY ITEMS: CONTROL VERSUS ALCOHOLICS

	Controls	Alcoholics	*P*-Values
Creatinine mg/ml (largely a measure of urine concentration)	2.03	0.97	0.001
Hippuric acid, chromatographic spot area/mg creatinine	0.20	0.27	0.01
Sodium mg/mg creatinine	2.26	3.25	0.001
Potassium mg/mg creatinine	1.09	1.99	0.001
Chloride mg/mg creatinine	3.89	5.94	0.001

Because urinary variations are larger and subject to more environmental influences, we place somewhat greater confidence in the blood data. The urine data appear meaningful, however, as shown by the statistical analysis and the fact that the urine data and the blood data are in agreement with respect to the status of about 95 per cent of the individuals, when they are judged on the basis of their "alcoholism indexes," described later.

With these data at hand, it seemed possible to devise a test which could be used to classify *individuals* as to their likeness or unlikeness to the alcoholic group as a whole. To do this, we have assigned to each of the values from each individual an "index number" which indicates how many half-standard deviations the value is on the "alcoholic side" of the control mean. In the case of every item except the urinary creatinine level, the high side is the "alcoholic side"; in this case the values from the alcoholics fall on the low side. Negative index numbers are assigned to values when they are on the opposite side of the control mean from the position of the alcoholic mean.

In order to compute the "alcoholism index" of each individual, we averaged the indexes for each of the twelve individual items listed in Tables 1 and 2. By this means we obtained composite indexes of from -1.8 up to $+2.4$ (average $+0.07$) for the control group, and from $+0.7$ up to $+8.3$ (average $+3.67$) for the alcoholic group. Only four controls had composite indexes of $+1.5$ or higher, and only two alcoholics had indexes lower than $+1.8$, so there was relatively little overlapping. If we were able to measure alcoholism-proneness successfully, it would not be surprising if we found among "non-alcoholic" individuals some who were innately more susceptible than some alcoholics whose training and environment had been conducive to the development of the disease.

To test the validity of the "alcoholism indexes," we have computed, without any adjustments, the composite indexes for 8 women (4 alcoholics and 4 controls), for whom we had collected data. None of these data, however, were used in establishing norms. On this basis the indexes of the four alcoholic women were 2.8, 1.8, 3.8, and 3.9, respectively, while the indexes of the control women were 0.1, 1.2, -0.6,

and 1.2. When this test based on data obtained from males was applied without change to females, we anticipated that the results might be less consistent than they were. It is apparent that alcoholic males and females have characteristics in common and that in these 8 female cases the test appears to be applicable.

To test further the validity of the "alcoholism indexes," we compared these individual composite indexes with independent "severity" ratings given groups of the same individuals, *40* and *29*, respectively, by an attending physician and a psychiatric nurse. These psychiatric ratings were from 1 for mild cases up to 5 for the most severe. The results showed that our alcoholism indexes and each of the psychiatric ratings correlated significantly; the P-value in each case was 0.05.

These facts point with a high degree of certainty to the conclusion that the items which we have measured are directly related to the disease alcoholism. A serious question arises as to whether the observed differences have to do with alcoholism-proneness or whether excessive alcohol consumption over a period of years has induced the same changes in the victims. While we are not in a position to answer this question with certainty, we can, on the basis of what we already know about individual patterns and their stability, indicate with confidence that alcohol consumption is not wholly responsible for the differences observed. Probably this factor enters appreciably into some of the measurements, but that it is minor is indicated by a large amount of general and specific evidence. The general evidence involves considerations of anatomy, composition, endocrine patterns, enzyme levels, excretion patterns, pharmacological responses, variable nutritional needs, etc., which have been summarized in the book *Biochemical Individuality*.[2]

Specific evidence that the hematological components of the test are genetically determined was obtained by Rosahn and Casey,[7] who studied five healthy men over a period of a year and six healthy rabbits over a period of two years and found that in each species there was statistically significant differences between the individuals with respect to red cell counts, total leukocytes, neutrophils, basophils, eosinophils, lymphocytes, and monocytes. They suggested that "each individual has a characteristic and typical blood formula which is largely determined by genetic factors." It is interesting that 80 per cent of the known alcoholics in our group could be correctly classified on the basis of our test, using only the three blood cell values which we determined.

In a doctoral dissertation which has not been published in detail, R. W. Shideler[8, 9] has found evidence by repeated analyses of samples from the same nine normal young men, that each individual exhibits a distinctive pattern with respect to the levels of sodium, potassium, calcium, magnesium, and phosphorus in saliva, plasma, red blood cells, and urine. With respect to most of these twenty items, there is clear evidence that certain individuals stand out as distinctly different from others. Here again the only adequate explanation is that genetic differences are responsible. Some may be inclined to dismiss urinary differences in mineral components by remarking that if one individual has more salt in his urine than another, it simply means that he has consumed more salt. There is nothing wrong with this statement except the word "simply." There must be physiological reasons, based, for example, on tremendous differences in adrenal cortices, why some "normal" people consume much more salt than others.

That the concentrations of various organic substances in urine vary widely from

individual to individual, even among babies, has been demonstrated in our laboratory[10, 11] over a period of years. In experimental animals the differences may be enormous, up to tenfold or more, when the animals are consuming exactly the same food. Closely inbred strains show many strong resemblances not shown by animals of heterogeneous ancestry, and it is evident that genetic factors are highly important. In human beings we know that some distinctive features of excretion pattern remain unchanged over a period of years—in one case that happens to have come under observation this was true even after a pregnancy and parturition. On the basis of these facts we regard the distinctive urinary levels as having a substantial genetic basis.

Underlying all these data is the fundamental fact, which is becoming clearer with the advance of biochemical genetics, namely, that gene differences (major or minor) give rise to enzyme differences in specific tissues, and these in turn must be largely, if not wholly, responsible for the basic differences in our individual body chemistries.

We do not take the position that our norms can be universally applied or that we have at hand a complete and dependable test for alcoholism-proneness which calls for no further investigation. Actually, there are several additional items not covered in this study which are at least promising: salivary sodium,[5] urinary uric acid,[5, 6] serum copper,[12] and serum amylase.[13] Uric acid requires further study with a completely reliable method. The elevated serum copper level (probably like a number of other individual items) is not specific for alcoholism. In this case elevated values are also found in pregnancy, schizophrenia, and a variety of infections.

We are of the opinion that the test for alcoholism-proneness as we have developed it can be applied immediately at the research level, and from such investigations a highly dependable test will develop. At the present time we regard the items we have measured as convenient earmarks rather than basic differences which necessarily have directly to do with alcoholism itself. In other words, we would consider it naïve to expect that lowering the respective levels in the blood and urine, even if it were possible, would constitute a cure of the disease. We suspect that when the crucial differences between alcoholism-prone and other individuals are found, these differences may involve large metabolic differences between specific structures which function in the regulation of appetites. What we have observed may well be minor metabolic reflections of these larger specific differences.

In conclusion we can say that, on the basis of accumulating evidence, we are of the opinion that alcoholism can probably be prevented even in severely alcoholism-prone individuals if they can be identified and if adequate account is taken of their nutritional needs, which may, for specific items, be far from the values commonly tabulated as satisfying the (hypothetical) standard or normal man.[14] Nutritional help may involve vitamin supplementation, but, in addition, other items such as minerals and amino acids (including glutamine[15]) must be considered.

We wish to acknowledge with gratitude the invaluable co-operation of the 57 alcoholics and the 45 controls, as well as the help of the superintendent and staff of the Austin State Hospital, and the following individuals who helped with analytical work: Ruth Kellogg, Douglas Kellogg, Edith Wilson, Ewa Abeman, and Ivan Roth. We are also grateful to Professors Wayne Holtzman, University of Texas, John Tukey, of Princeton, and Dr. Jerome Cornfield, of the U.S. Public Health Service,

who gave statistical advice but who should not be held responsible for the exact procedures which we utilized.

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AN EXAMPLE OF A NONNORMAL DISTRIBUTION WHERE THE QUOTIENT FOLLOWS THE CAUCHY LAW

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Let x and y be two independently and normally distributed variates with zero means and the common variance; it is then well known that the quotient x/y follows the Cauchy distribution symmetrical about zero. It has been conjectured that this is a unique property of the normal distribution and that it is possible to obtain a characterization of the distribution by this property. In the present note we show that this conjecture is not true, and we give below an example of a non-normal distribution where the quotient has the Cauchy distribution. This example, of course, does not rule out the possibility of characterizing a wider class of distribution laws by this property of the quotient.

EXAMPLE: Let x and y be two independently and identically distributed random variables, each having an absolutely continuous distribution function symmetrical about zero. Let the probability density function of x be given by

$$f(x) = \frac{\sqrt{2}}{\pi} \cdot \frac{1}{1 + x^4} \qquad (-\infty < x < +\infty). \tag{1}$$

We introduce the polar transformation $x = r \cos\theta$, $y = r \sin\theta$ and can easily deduce that the joint probability density function of r and θ has the form