*INDIVIDUAL METABOLIC PATTERNS, ALCOHOLISM, GENETOTROPHIC DISEASES**

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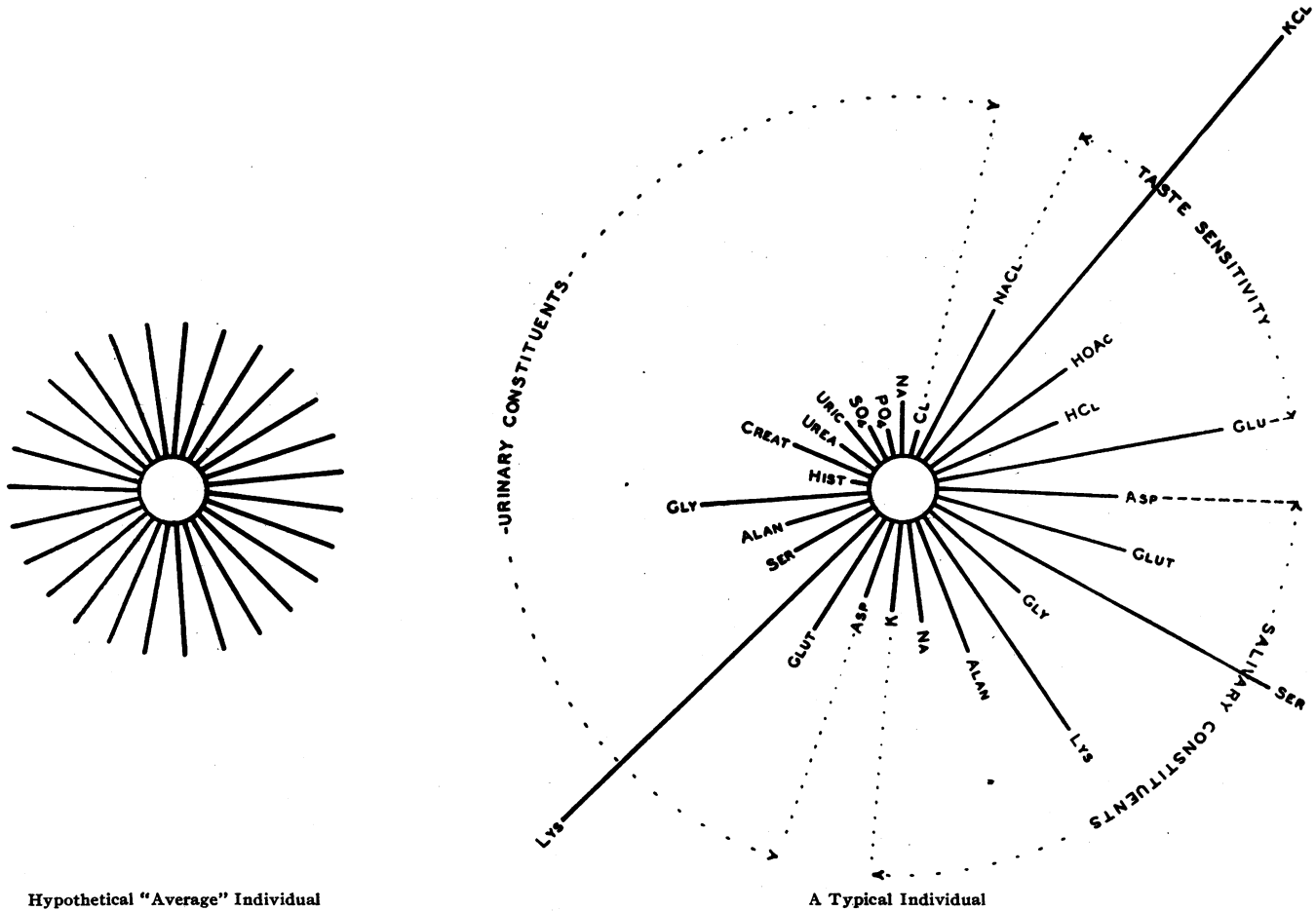
At the 1948 Annual Meeting of the National Academy there was presented preliminary evidence indicating that each individual possesses what may be called a "metabolic personality"—that is, a distinctive pattern of metabolic traits.[1] The existence of these distinctive patterns is established by analysis of body fluids and of physiological responses to chemical stimuli and is exemplified in figure 1. At the left is graphed, using polar coördinates, various metabolic traits of the "hypothetical average individual" whose every trait is the average of his fellows. At the right is graphed on the same scales the metabolic pattern of a typical real individual in which many traits vary widely from the average. This pattern is a relatively consistent one and is maintained for this individual at least over a period of several months.

The hypothesis was set forth that the metabolic patterns of individuals are of great import in the lives of the individuals who possess them, not only with respect to susceptibility to disease, but also with respect to nutrition, sex, mental abilities and many other facets of their lives.

Today we wish to present further and more specific evidence with respect to how these metabolic patterns are of moment in connection with the specific problem of alcoholism. This evidence is based primarily upon animal experimentation, the background of which is described elsewhere.[2-4]

It should be noted at the outset that individual animals in an ordinary laboratory colony have distinctive metabolic traits just as do the members of a human population. In order to conserve space we will not present data to substantiate this statement. When such animals are placed in individual cages and are continuously given a choice between water and 10% alcohol (the positions of the two drinking bottles being switched daily), they exhibit individual patterns with respect to alcohol consumption. Some drink fairly heavily beginning perhaps the first day the alcohol is offered. At the other extreme, some continue to abstain for an indefinite period of time. Intermediate between these are those that drink very moderately for an indefinite period of time and those that drink very little at first but after a few weeks drink relatively heavily. Some individual animals exhibit a relatively steady consumption day after day; in others the consumption fluctuates widely. (Figure 2)

These individual patterns of alcohol consumption are genetically con-



Hypothetical "Average" Individual

A Typical Individual

FIGURE 1

The following abbreviations are used in Figure 1: Creat = creatinine, Uric = uric acid, Hist = histidine, Gly = glycine, Alan = alanine, Ser = serine, Lys = lysine, Asp = aspartic acid, Glut = glutamic acid, Glu = glucose.

trolled as is evidenced by the fact that each strain of animals appears distinctive with respect to its alcohol consumption records. We have tested in a preliminary way three strains of mice and two strains of rats. Possibly more important evidence is the fact that when a closely inbred strain of mice resulting from the continuous use of brother-sister matings was tested, all the animals exhibited substantially the same pattern of

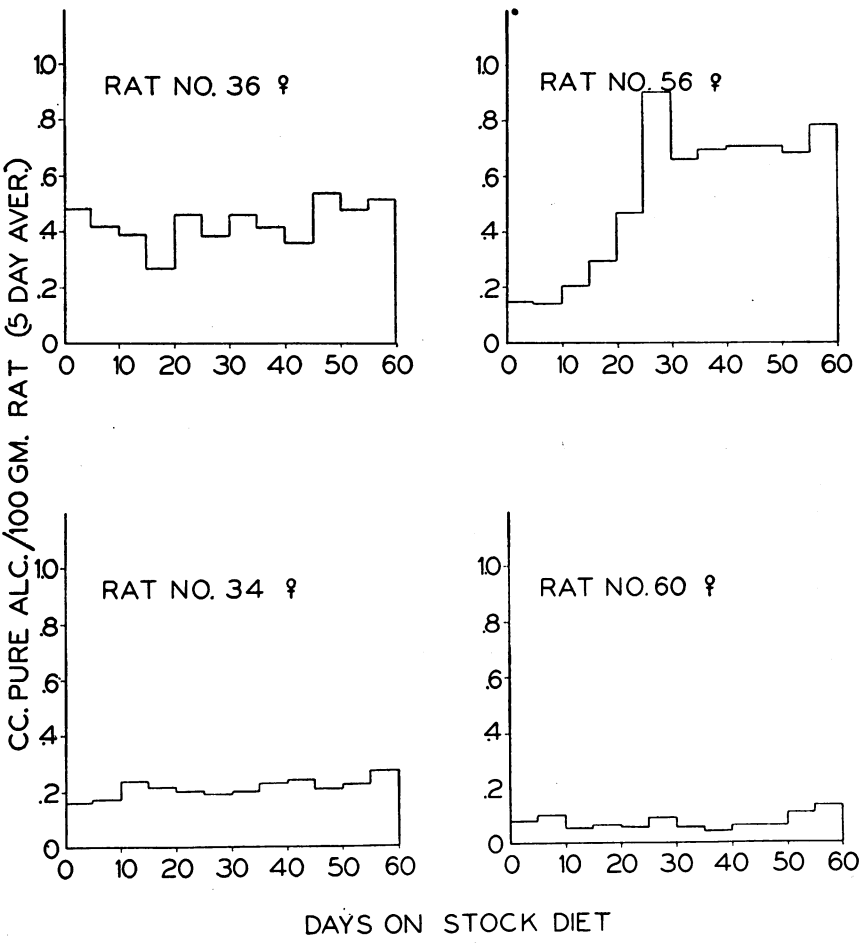


FIGURE 2

response. Further convincing evidence on this point was obtained when the different strains of animals were tested while on different diets.

There has been a far-reaching and, we believe, disastrous tendency not only on the part of social students and educators in general but also to a degree among the medical profession to avoid the possible importance of heredity as a factor in any major human problem. The attitude can be

expressed something like this: "If a certain disease is hereditary, or if mental traits and abilities are hereditary, nothing can be done about it. Therefore, let us assume that diseases are rarely hereditary and that every normal person is capable of unlimited development in almost any direction."

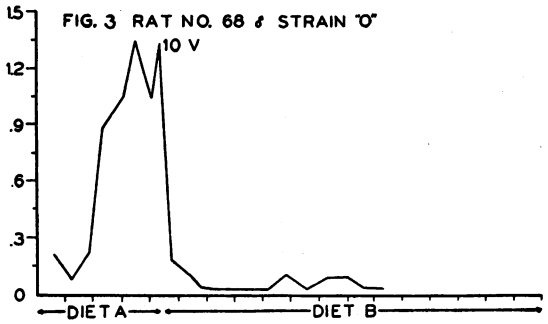
How wrong this attitude is will be amply illustrated if the results of our animal experiments are substantiated by human experience. Whereas our experiments have fully convinced us that the tendency of individual rats to consume alcohol is genetically controlled, this does not mean at all that nothing can be done about it. On the contrary, on the basis of somewhat unusual dietary considerations we have been able to abolish with surprising regularity the appetite of rats and mice for alcohol, even though it is clear that each animal has its genetically controlled metabolic peculiarities and that different factors in the treatment are effective for the different animals.

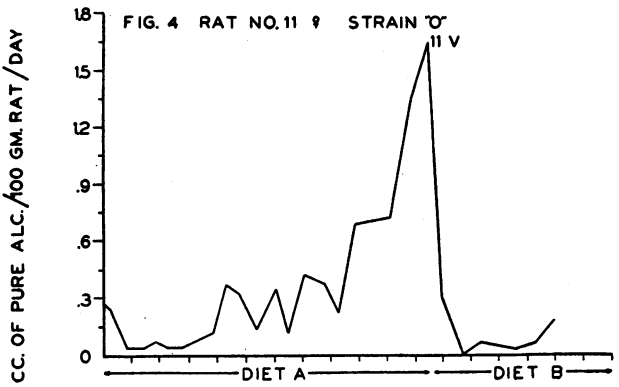
In Figures 3, 4 and 5 are depicted examples of the scores of rats which have been similarly affected. Rat No. 68 had his appetite for alcohol abolished by the simple oral administration of 10 known B vitamins. We do not know how many or which ones of the B vitamins were responsible for the effect in this particular rat. We do know, however, that only a small percentage of rats will yield to this treatment.

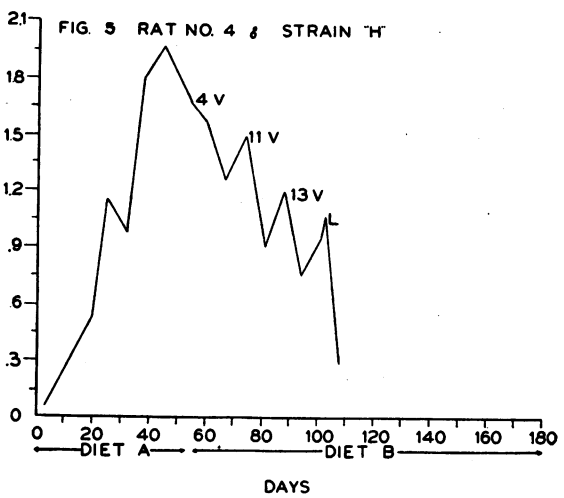
Rat No. 11, Figure 4, is one which responded, however, when in addition to the 10 B vitamins the antipernicious anemia vitamin was administered by injection. This treatment was found to be effective for 17 out of the 24 rats of our original laboratory strain, to which it was given. When the same treatment was given to 45 rats of a strain which we obtained from a neighboring laboratory, only 3, or 7%, responded. The consumption curve of rat No. 4, Figure 5, exemplifies the finding that for some rats vitamin A deficiency is a factor in the development of an appetite for alcohol. Thirty-one rats, whose consumption curves were relatively high, were administered vitamin A in addition to other supplements previously given, with the result that every single one showed immediately a decreased consumption.

The same curve shows that something in linseed oil—presumably linoleic and linolenic acids—is also a factor. Like a number of other rats, this one remained at a relatively high level of consumption even after the administration of 13 vitamins. When some linseed oil was included in the diet the consumption promptly fell to a low value.

Our experimental studies lead us to conclude that we can by dietary control keep all the rats in a colony from consuming alcohol when it is furnished *ad libitum* under our conditions. Even an initial experiment in this direction, made before we were acquainted with the effects of the antipernicious anemia vitamin, vitamin A or unsaturated fat acids, caused







Diet A is deficient in B vitamins. Diet B is the same except for added B vitamins. *4V* = thiamine, riboflavin, calcium pantothenate and folic acid (Folvite). *10V* = same as *4V* with addition of pyridoxine, choline, inositol, *p*-aminobenzoic acid, nicotinic acid and biotin. *11V* = *10V* with the addition of antipernicious anemia liver preparation given intraperitoneally. *13V* = *11V* with the addition of vitamins A and D. *L* = *13V* with the addition of linseed oil.

in a group of rats a decrease in consumption down to $^1/_7$ of the original.

We are also convinced that after an appetite for alcohol has been developed, it can be abolished in all rats by a use and extension of the method we have employed.

Out of these observations we have developed a theory of alcoholism which appears to be sound on the basis of all tests we have been able to apply. According to this theory, alcoholic craving which develops in compulsive drinkers constitutes a perverted appetite which arises as a result of one or more dietary deficiencies. Little is known as to how special appetites and cravings develop, but that they arise from the internal physiological environment has been amply demonstrated in a number of cases.

The dietary deficiencies in alcoholics arise not primarily because of failure to eat what is regarded as satisfactory food, but because the genetic patterns of these individuals are conducive to the development of crucial deficiencies. Partial genetic blocks which have recently been investigated at the California Institute of Technology[5] are thought to be responsible. When there is a partial genetic block, the capability of producing a specific enzyme is not entirely lost, but it is impaired to such an extent that there develops an augmented nutritional requirement which may be for a specific vitamin, amino acid, mineral element or other metabolic substance.

It is hoped that for the treatment of alcoholism in human beings a "shotgun" therapy may be developed which will effectively curb or abolish the excessive appetites of many compulsive drinkers.

Before treatment of alcoholics can be placed on a satisfactory basis, however, much more needs to be learned about individual metabolic patterns and what specific deficiencies are most often associated with the disease.

Out of this theory of alcoholism and the laboratory findings which support it we have developed the concept of genetotrophic disease (geneto = genetic; trophic = nutritional). A genetotrophic disease (of which we believe alcoholism is an example) is one arising fundamentally from nutritional deficiency which in turn has its basis in a genetically controlled augmented requirement for one or more specific nutritional elements. Other factors may enter to complicate or aggravate such a disease.

It suggests itself to us with great force that probably many diseases which have an obscure etiology may be essentially genetotrophic in origin. Among the diseases in which genetotrophic factors are probably involved in an important way are allergies, mental diseases, cardiovascular diseases, arthritis, multiple sclerosis and even cancer. This is hypothesis, of course, but it is based upon a large body of data.

Let us look for a few minutes at the tremendous problem of mental

disease which has received wide-spread and well-deserved popular attention in recent years.

If we consider an example of a specific, important type of mental disease—schizophrenia—we are confronted by irresistable evidence that it has physiological concomitants. If we take a one-sided view, we will assume *a priori* that the physiological disturbances are psychogenic in origin and are a result of mental derangement. If we look at the problem more broadly, however, we will consider the possibility that mental derangement may be the result of physiological impairment. We believe there is abundant reason for investigating this latter possibility.

We have made a preliminary study of the metabolic patterns of a considerable number of patients of the Austin State Hospital. This study has revealed the existence among these patients of a number of metabolic traits which are either absent or rare in the well population. We are of the opinion that some of these traits will be found to be important in connection with the causation of mental diseases, and that such investigations need to be greatly extended.

The possibility that mental diseases are genetotrophic in origin or that they have genetotrophic factors in their etiology cannot be brushed aside lightly in view of the known fact that certain mental difficulties have been treated with remarkable success by physiological means. I refer to the severe mental difficulties that sometimes accompany menopause which can be completely dispelled by hormone therapy, and the mental derangement accompanying pellagra which can be cured by dietary means.

The recent survey by Kallmann[6] gives what appears to be practically irrefutable evidence that schizophrenia has a genetic basis. This by no means indicates that nothing can be done about it. When and if we find that certain metabolic difficulties are at the basis of the trouble, there is, we believe, an excellent chance that a way out can be found. If genetotrophic factors are found, as seems highly probable, certainly help can be given.

In any event the physiological approach to the study of mental disease needs far more emphasis than it has so far received. We cannot afford to turn the problem over to cultists or to those who are wholly unprepared for physiological exploration.

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