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John S. Allen, Vincent M. Sarich

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SCHIZOPHRENIA IN AN EVOLUTIONARY PERSPECTIVE

*JOHN S. ALLEN and VINCENT M. SARICH**

Introduction

Schizophrenia is at once one of the most fascinating and frustrating aspects of the human condition. The "schizophrenia problem" has been studied by physicians, psychiatrists and psychologists, neurologists, epidemiologists, sociologists, cultural anthropologists, geneticists, and biochemists. Although some claim that schizophrenia has a recent origin in human populations [1, 2], it is generally accepted that schizophrenia has existed throughout human history [3, 4]. The overwhelming majority of workers in the field now agree that schizophrenia is a condition with a strong genetic component in its etiology: a schizophrenic *genotype* (or *genotypes*) exists. But no one would argue that the expression of the schizophrenic *phenotype* is dependent solely on the genetic factors; concordance studies in identical twins make it clear that ontogenic factors, involving both the genic and cultural environments, play an important role in the character of the expression of the schizophrenic genotype [5–9]. Because of this fact—one that would, in varying degrees, apply to any behavioral condition—casting the debate in the form of a nature/nurture argument trivializes it into barrenness at best, and into counterproductivity at worst.

Although it is often said that schizophrenia occurs at a frequency of about 1 percent worldwide, it should be recognized that this figure is an

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*Department of Anthropology, University of California, Berkeley, California 94720.

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average and that there is considerable interpopulational variation in schizophrenia prevalence [10, 11]. Indeed, it would be very odd for any low-frequency condition with genetic involvement to manifest itself at uniform rates in all human populations. In the case of schizophrenia, Eaton's review [11] shows that there is about a tenfold variation in point prevalence rates. Using the 1 percent figure as a guide, and given the reduced fertility of overt schizophrenics [12], it follows that the schizophrenic genotype is being maintained in human populations at a frequency far greater than mutation rates would allow. This suggests that schizophrenia poses an interesting evolutionary problem—a fact first recognized by Huxley, Mayr, Osmond, and Hoffer [13].

The Beginnings of an Evolutionary Perspective

Evolutionary biology may therefore provide one approach to solving some aspects of the schizophrenia problem. While it would be misleading to state that the evolutionary perspective has never been applied in the study of schizophrenia [12–19], it is fair to say that it has had little or no influence on the conventional thinking about schizophrenia. There are a number of reasons for this. First, most investigators in the field have quite understandably had a clinical, sociological, or cultural orientation, and in none of these areas is an evolutionary perspective either common or especially welcome. Clinical thinking is necessarily typological, and we note that the typological approach has provided only a limited understanding of normal human variation. Second, the biological and genetic bases of schizophrenia, prerequisite knowledge for evolutionary studies, have only been established relatively recently (and imperfectly—see [20] for an overview). Third, evolutionary thinking is often perceived more as a hindrance than a help in studies concerning the modern human condition. For example, Gottesman and Shields state:

> We agree . . . that it is not too helpful to rely on evolutionary theory in deciding among genetic models; we simply do not know enough about how any human behavior evolved. . . . Attempts at invoking evolutionary (pseudo-) explanations for either the origin or perpetuation of schizophrenia may be futile and useless, muddling the line of genetic reasoning. [7, p. 225]

This statement directly and indirectly reflects a number of misconceptions concerning the evolution of human behavior in general and of schizophrenia in particular. In reality, we can come to understand a great deal about the evolution of human behavior using information and insights from a number of areas. To begin with, comparative studies using other species can help us to differentiate between those aspects of human behavior that are derived and those that are primitive. Then,

studies in paleoanthropology, paleoecology, and paleopathology, aided by an archeological record spanning 2 million years and three or four hominid taxa, and complemented by knowledge of morphological and behavioral correlates in extant species, give us information concerning the environment, diet, and behavior of our ancestors. Finally, and most important, we have a rich cross-cultural data base that amply demonstrates the extent and limits of human behavioral variability. Our knowledge of the evolution of human behavior is far from complete, of course; whether or not we "know enough" to study the evolution of any particular behavioral trait is in large part dependent on the results of studies carried out to test explanatory hypotheses.

There is also a prevalent notion that to study the evolution of schizophrenia, or any other behavioral trait, we must first fully develop our understanding of its current condition and only then consider its evolutionary history. We view this approach as representing a wholly artificial and particularly counterproductive separation between complementary and interactive areas of inquiry; once the potential adaptive importance of a trait is indicated, complete understanding of the trait requires, and is facilitated by, putting it into an evolutionary context. For example, although the schizophrenia phenotype can with a high degree of confidence be identified in different cultures [21], there is still a question about whether schizophrenia represents an etiologically unitary or heterogeneous condition. Evolutionary studies could offer insights into determining the relative importance or solution of this problem. An etiologically heterogeneous group of genetic variants of various red cell components (including hemoglobin S, various thalassemias, and G6PD deficiency) appears to be unified by the fact that they are selected for (i.e., increase fitness) in malarial environments. These variants produce a common phenotype, one in which the red cell environment is less favorable for *Plasmodium falciparum* [22].

Gottesman and Shields ask that the pure line of "genetic reasoning" not be clouded by "pseudo-evolutionary explanations." Their view is that "schizophrenics could be thought of as part of the genetic load of our species, the price paid for conserving genetic diversity" [7, p. 225]. Genetic load explanations are, of course, as "evolutionary" as those based on selection; they are also not very amenable to direct or indirect testing. It seems to us that any human condition with genetic involvement and negative effects could be "explained" through a genetic load argument. But having made such an argument, we cannot see how our understanding of the condition is in any way advanced. While there is no doubt that we "pay a price" for conserving genetic diversity, the price must be paid every generation, while the payoff for the maintenance of the diversity—greater adaptive flexibility and potential—generally lies

in the future. We address ourselves throughout this paper to identifying the currency in which today's price is being paid, and that in which it was paid in the past.

Genetic Models and Scientific Strategies

At this time, any number of genetic models can be made to fit any number of pedigree data sets (see, e.g., [23–26]). We note that the study of, for example, morphological traits, makes it clear that selection operates on polygenic as well as monogenic systems. Our discussion will not be dependent on the correctness of some particular genetic model; however, we will point out some problems we have with the "multifactorial threshold model" of Gottesman and Shields (recently discussed by McGue, Gottesman, and Rao [25]). The multifactorial threshold model says that schizophrenia is relatively common because it is part of the genetic load of our species (an argument we have just characterized as seriously flawed), and it also takes the 1 percent average risk of schizophrenia in populations worldwide as a uniform risk. However, as we have already noted, prevalence rates for schizophrenia show substantial interpopulational variation. In addition, schizophrenia is widely, and in our view, correctly, perceived as a "disease of civilization" [2]. The multifactorial model can account for the interpopulational variation of schizophrenia only if it views the norm of reaction of the schizophrenia genotype as sufficiently broad, such that, in the environment of a simple society, behavior seen as pathological by that society is much less likely to occur than in the environment of a complex society. However, a corollary of the multifactorial threshold model, developed, it should be noted, in the context of a single complex culture, is that the norm of reaction for schizophrenia should be relatively narrow. McGue, Gottesman, and Rao [25, p. 1173] state that the "transmission of liability to schizophrenia could be accounted for by genetic factors only. . . . Cultural transmission, should it occur, does not appear to be a major contributor to liability." Therefore, the multifactorial threshold model does not adequately account for interpopulational variation in schizophrenia incidence rates—nor, in avoiding concern with what is being selected for, does it provide any real explanation for the relative abundance of schizophrenia we see in the world today.

We also believe, and this is probably an even more important point, that a serious error in scientific logic and strategy is committed by going to a multifactorial model before exhausting the possibilities of simpler, single-factor models. While we have no doubt that various genetic loci as well as various ontogenetic factors are involved in the production of overt, dysfunctional schizophrenia, we are equally certain that the vari-

ous factors do not have equal effects. Thus we do not even try to "explain" the entirety of the schizophrenic condition by genetic variation at a single locus. We do hope to learn, however, how much of it is explicable in terms of single, identifiable, and isolable factors, and how much by interactions between and among them.

Schizophrenia as a Balanced Polymorphism

Following Huxley et al. [13], we propose that the schizophrenia genotype (or genotypes) is maintained in human populations as a balanced polymorphism of some sort. The decreased fitness of overt schizophrenics *must* be balanced by a corresponding increase in the fitness, relative to the population as a whole, of individuals who carry the gene (or some part of the polygenic complex), but who do not manifest the pathological condition. We emphasize that these carriers must be doing better than average; just doing as well as the rest of the population could not replace those genes lost through the reduced fertility of their overt, dysfunctional relatives. We should point out at this time that studies attempting to demonstrate higher-than-average fertility in the relatives of schizophrenics have been inconclusive [7]; however, as discussed by Kidd [19], an absolute selective advantage in the relatives of on the order of 5 percent would be perfectly adequate for the maintenance of the polymorphism and yet be difficult, if not impossible, to demonstrate. Selective advantages of that magnitude would be particularly difficult to demonstrate in slowly growing or stable populations that show low variance in fertility. The classic example of a balanced polymorphism in human populations is sickle-cell anemia [27], where the sickle-cell heterozygote is protected against falciparum malaria. We do not believe that schizophrenia follows this classic heterosis model.

We reject the heterosis model at the outset from some basic considerations. First, pedigree (especially identical twin) studies indicate that the risk of becoming an overt schizophrenic even with the same genotype as an already overt schizophrenic is only about one in three. This, it should be emphasized, is for a situation where the genetic differences are nonexistent, and the social/cultural effects are as similar as possible. More typically then, the risk factor for an individual with a "schizophrenia genotype" is perhaps more like the one in five or so suggested by other pedigree studies [28]. Figures of this sort make it difficult to impossible to sustain the heterosis model, at least in its simplest form, as the figures simply will not add up. If, as many seem to think, there are three fundamental genotypes involved (*NN* = "normal"; *SN* = schizophrenia heterozygote of increased fitness; *SS* = about a one in five risk of becoming an overt schizophrenic), then how could the risk for the child of a schizo-

phrenic mother be the roughly 10–14 percent reported? If she were *SS*, to have half her children *SS* (and, therefore, about 10 percent overtly schizophrenic) would require that the fathers be drawn from a population where the *S* allele frequency was at least 0.5 with no reduction in fertility for the putative *SS* males. The latter is clearly untenable, as is the implication that the frequency of *SS* individuals in that population would be at least 0.25 and therefore at least 5 percent overt schizophrenics. We include this discussion only as an attempt to wean readers who may be willing to take the evolution/genetics scenario seriously away from the "schizophrenic homozygotes/schizoid heterozygotes" perspective that seems to be so common in our experience. That perspective is, it seems to us, unduly deterministic and fatalistic in its implicit acceptance of a "one genotype–one behavioral phenotype" view of a situation that would appear to be appreciably more subtle and complex than that. Multilocus models that avoid these problems can be formulated but are, as already noted, very difficult to test and make use of, and we see no necessity for their consideration at this time.

A Population with Schizophrenics Is, at Some Level, Two Populations

We argue that the identical twin data in particular clearly allow—one might almost say, require—serious consideration of a model where the population is divided into just two groups: those with the schizophrenia genotype and those without. We note that a society composed entirely of schizophrenics could not exist—that would be a clear oxymoron. Nor could a society with a high proportion of schizophrenics exist; selection would operate within social groups to keep the number of schizophrenics and their relatives at "manageable" levels. But, as we have already noted, the loss of schizophrenia genes owing to the lowered fertility of overt schizophrenics must mean that those same genes are affording advantages to other individuals, and we suggest that those other individuals do not differ, with respect to the schizophrenia genotype, from the overt schizophrenics. The critical point will not turn on the precise molecular biology/genetics details of the situation, whatever they may turn out to be, but on the recognition of the condition we know as schizophrenia as representing one aspect of a balanced polymorphism—most likely of a frequency-dependent type [29, 30]. Balanced polymorphism concerns force us to consider the positive aspects of a condition; clinical investigations by definition focus on the negative. It is from that antinomy that we proceed.

The evolutionary biologist looks at a condition such as schizophrenia and reasons as follows:

1. The condition has negative aspects that serve to decrease the individual fitness of overt schizophrenics.
2. Schizophrenia appears to be unique to our species.
3. There is a clear genetic/biochemical involvement, though
4. pedigree (especially identical twin) studies demonstrate that there must be environmental involvement as well in the production of the negative dysfunctional phenotype.
5. That phenotype is present at frequencies which rule out any possibility of maintenance by mutation pressure alone. Therefore,
6. the schizophrenic genotype or genotypes must lead to a range of behavioral phenotypes of which only some result in lower social and reproductive fitness, while others must in fact increase them (or have increased them in the very recent past). Thus,
7. the evolutionary focus is on schizophrenia as a condition, and not simply as a disease process. We emphasize that positive aspects relating to the schizophrenic condition must exist and that they may be an integral part of the human condition itself.

Huxley et al. [13], Erlenmeyer-Kimling and Paradowski [14], Erlenmeyer-Kimling [15], and Carter and Watts [16] all postulate that the relatives of schizophrenics, and schizophrenics themselves, possess some kind of "physiological advantage": resistance to injury, resistance to viral infection, greater healing abilities, or even being less accident prone. These hypotheses are not yet well supported, and they have not been reconciled with the biological/cross-cultural distribution of schizophrenia. If schizophrenia does confer some physiological advantage, it should be particularly evident in terms of the biocultural distribution of the condition, and we see no evidence of this [31]. We suggest that a physiological advantage possessed by schizophrenics, if it exists at all, is of secondary importance in the maintenance of the genotype in human populations. Viewing the situation within evolutionary and human variation perspectives, it seems far more likely that the "schizophrenic advantage" will be found somewhere in the behavior of schizophrenics. As we are all aware, selection works on the phenotype, not on the genotype. We know that the schizophrenia genotype sometimes has a marked behavioral phenotype, and we therefore choose to look at how selection might operate on the behavior of schizophrenics and their relatives. We are, therefore, not going to concern ourselves directly with mechanisms, biochemical or environmental, of the expression of schizophrenia, though this is not to say that the results of evolutionary studies cannot shed light on mechanistic or etiologic problems. In fact, we expect that, as we attempt to answer questions concerning the phylogenetic, evolutionary "why" of schizophrenia, we will gain insights into its developmental processes as well.

The Schizophrenia Genotype Contributes to Variation Found along the Dimension of Sociality

We recognize first that there are no behaviors in any real sense unique to the schizophrenic condition. What is characteristic of the condition is that certain behaviors or sets of behaviors occur far more, or far less, often—or to significantly lesser or greater degrees—than is characteristic for the rest of the population, and/or they occur far more often at inappropriate times and in inappropriate circumstances. Such behaviors most typically involve one or more of the following: difficulties in forming and maintaining social relationships caused by, or leading to, a marked asociality; a fixation on self leading to a solipsistic view of the world; flatness of affect characterized by an inability to enjoy life in general, or even particular aspects of it, and/or by the lack of a sense of humor and by a compulsive single-mindedness; intense suspiciousness often crystallizing as full-blown paranoia or its negation, catatonia; hearing voices and talking to oneself excessively; and an unusual susceptibility to delusional views of self and the rest of the world. We note parenthetically that delusions common to the population as a whole (such as beliefs in a god or gods, or in the afterlife, or in a particular creation myth) do not count as such when considering whether a particular behavior pattern is unduly delusional.

Now that is a rather full list to choose from in our search for some evolutionary basis for the schizophrenic condition. What we are looking for is some reasonable, testable hypothesis in which one or more of these behavior patterns, in something short of the pathological state, can be seen as conferring increased fitness on the individual exhibiting them.

One hypothesis that has been suggested in the past is that schizophrenics could adapt to life in simpler societies by filling the role of shaman or mystic [32–34]. Although this is really a theory of social adaptation, it can easily be extended to, and be seen to have implications in, the biological realm. We agree with Torrey [2] and Peters and Price-Williams [35] that it is highly unlikely that schizophrenics typically filled such high-status roles as shaman, healer, or religious leader, as equating shamanistic behavior with schizophrenic behavior ignores several cogent facts. First, the culture or drug-mediated visions of the shaman tend to be stereotyped within cultural bounds, while psychotic delusions are both highly idiosyncratic and more universal. Second, a shaman must be able to initiate, and often terminate, his experiences at will; these are capabilities a schizophrenic does not have. Third, a shaman, almost by definition, must be socially adroit, and this too is a skill lacking in most schizophrenics. Finally, the social importance of the shaman (or mystic, or religious leader) probably imposes severe limitations on the variability in that role which will be tolerated by society; again, one has difficulties

in seeing the schizophrenic as being able to accept, and be effective within, such limitations.

Creativity has also been suggested, most notably by Karlsson [17, 18] and anecdotally by Heston [36], as the social/behavioral advantage possessed by the relatives of schizophrenics. Although we emphasize that we do not in any sense deny the potential importance of creativity as a factor in the maintenance of the schizophrenia genotype, we see it as a relatively infrequent result of a much more mundane phenotype. Creativity as such is, after all, not particularly well rewarded in human societies, nor are cultural innovations particularly welcome. As Karlsson and Heston point out, the normal relatives of schizophrenics may be more likely found in more creative occupations; and we add that there is little doubt that truly creative individuals are much more likely to become overtly schizophrenic (whether or not institutionalized) than is true for the population as a whole. This, however, is not sufficient evidence that creativity alone, or even in major part, is responsible for the spread of the schizophrenia genotype. We know from recent history that cultural innovations can have a marked accelerating effect on the rate of cultural evolution—and that such events are few and far between. We cannot see them at all in the Paleolithic, except perhaps at the time of the emergence of modern *Homo sapiens* around 40,000 years ago, and one would certainly expect that creativity would have a utility very much positively correlated with cultural complexity. Thus it is difficult to imagine any significant fitness advantage that might have accrued to exceptionally creative individuals throughout virtually the entire existence of *Homo*.

It seems to us that the best place to look for the schizophrenia advantage is in the somewhat touchy relationship between the individual and his culture and society. We often forget that a social existence does not necessarily represent an evolutionarily stable strategy [37], and we need look no further than two of our closest living relatives, the orangutans and the gibbons, for exemplars. Orang "social grouping" consists of a solitary male defending a territory occupied by a variable number of dispersed females with their young; gibbons live in nuclear families consisting of a pair-bound male and female and their immature offspring [38]. Both lineages long ago abandoned the truly interactively social existence that their forebears undoubtedly possessed. Individuals necessarily give up something of their individuality when living in an interactively social grouping, and while they must ultimately get more back than they gave up to the group (or the group would not be maintained over time), there is always the loss of a certain degree of individual autonomy and freedom of action. Thus one can imagine marginal increases in fitness accruing to those individuals who are able to shift their own position in the relationship shown in figure 1.

We suggest that the individual in a group has no rights and privileges

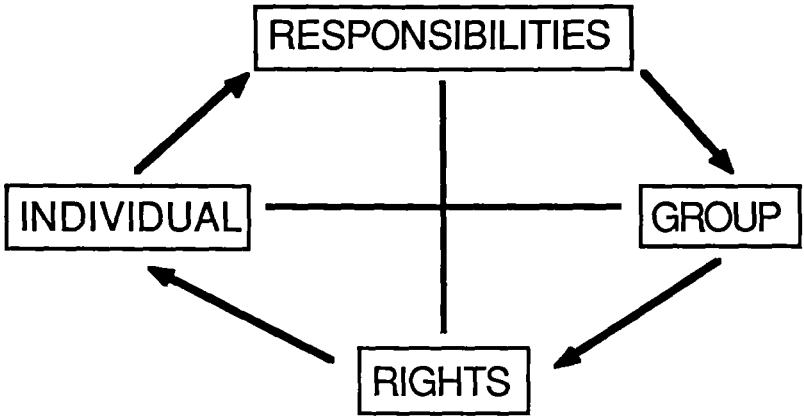

FIG. 1.—The lines joining individual and group, and rights and responsibilities, are meant to indicate that the two members of each pair are functionally, and inextricably, linked in our species. Humans must live in social groups, and there cannot be rights without corresponding responsibilities. While there can be no doubt concerning the former, there are many who see certain rights as "inalienable"—though, of course, the vision as to which those might be depends very much on the society in which it is being made. But if certain rights are indeed inalienable, one has to ask from where they derive and, in particular, who denotes and defends them? Clearly, the only possible answer to each of those three questions is that it is the society in which the individual lives. Thus the rights granted to the individual by his society must, in some very real sense, be paid for by the responsibilities to the society fulfilled by the individual. It is this logic that leads to the indicated directionality.

beyond those granted by that group, while membership in the social unit requires assumption and fulfillment of numerous responsibilities. Individuals who succeed in withholding some of their responsibilities to the group, while simultaneously maintaining good standing within the group, may be the ones who accrue marginal increases in fitness. One can see that, if the group is to be maintained, this must necessarily be a frequency-dependent situation.

Human societies, of course, differ markedly in where they see the rights/responsibilities balance as developing, but there can be no question of the supremacy of the group in any individual-group conflict. Given this fact of social life, we can infer that very strong selective factors must have operated throughout primate history to instill into the genes of individual primates a desire for, and ready conformity to, a social existence. One need not be a profound student of the human condition to note that sociality is one of those things, like bipedalism and language, that young humans learn without being taught; one can therefore conclude that we have genes for sociality that are expressed through normal ontogenetic development. This is, however, development into a social and cultural milieu far richer and complex than that of any other primate species, living or extinct.

Schizophrenics represent the extreme end of human variation on what might be termed a "sociality scale." As noted above, the overt schizophrenic may be paranoid or catatonic; either, in milder form, may be manifested as simple asociality. An asocial, or less social, person is one more likely to operate outside the narrow guidelines of the status quo; more likely to isolate himself from, or reject, the shared knowledge and worldview of the social group. Such rejection and isolation may make the role a difficult one to play, but they also increase the likelihood of being able to question, and reject if necessary, the shared biases and misconceptions of the group. Actual creativity, we feel, will be the exceptional result rather than the rule. What has been selected for—in the nonpathological possessors of the schizophrenia genotype—is simply the ability to take back a bit of the individuality surrendered to the group during tens of millions of years of evolution of interactive sociality in our lineage.

We fear that the point we are trying to make here may suffer from being seen as unduly subtle; that the taking back of a little individuality is rather mundane in comparison to other suggestions such as heightened creativity with genius as the end, or the increased suitability for filling roles such as shaman, mystic, or religious leader. While we do not deny that possessors of the schizophrenia genotype(s) might in fact be better suited for some of those roles and recognize that those roles have an undeniable appeal to our species, we nevertheless doubt that selection for these roles could represent a significant force in human evolution. We are thus left with the notion of a genotype that leads to the perhaps mundane phenotype of markedly increased asociality. As our ancestors made a greater and greater commitment to an interactively social existence (it is likely that, once language came in, adaptive options such as those chosen by the gibbon and orang lineages were no longer available), there would have been an increasingly fit role for the individual who could, to a greater extent than most, resist the collective view of things. A delicate balance develops at the individual level between being just different enough and being too different; and at the populational level between having a beneficial number of "different individuals"—a source of variability and, occasionally, creativity—and having too many, which would destabilize the social existence itself.

This seemingly mundane shift along the sociality axis is, for example, particularly easy to see in the academic world: many academics have achieved their positions precisely because at some point they have been able to examine and reject the prevailing opinions (and holders of those opinions) in their fields. This is not something especially easy to carry off for most people, and in addition, it is all too easy for some to come to feel that most everyone else is wrong most of the time. The former can lead to "creativity"; the latter, to a solipsistic paranoia. All too often the same

individual may find it difficult to consistently judge in which of those realms he may be at any given time.

A society of schizophrenics is the classic oxymoron; thus this may be a textbook case of a frequency-dependent polymorphism. This model also demands that, at the individual level, we see the overt schizophrenic as one who simply cannot "handle" the condition in a productive fashion. That is, we would not draw a line between the overtly psychotic and the "normal" but between those who carry the schizophrenia genotype and those who do not. Among those who do, there will be a balance between those who can "handle" the condition productively and those who cannot. This balance, given the clear reduction in reproductive fitness of overt schizophrenics, must be heavily biased toward those who can in fact take behavioral advantage of possessing the genotype. This brings us to the frequency-dependent aspects of the situation. Presumably, any given social/cultural context can tolerate and make use of a more or less set amount of individuality. As the number of carriers of the schizophrenic genotype increases, then, the increased fitness available to any one of them will necessarily, at some point, begin decreasing. Once the marginal gain equals the loss of fitness experienced by the overt schizophrenics produced, we are at the balance point.

Testing the Evolutionary Hypothesis: Physiological Response Tests and the Cross-Cultural Distribution of Schizophrenia

The hypothesis outlined above seems, to us, to make a good deal of sense, but making sense is by no means the same as being correct. Any worthwhile hypothesis must have productive and testable corollaries. We begin with the critical question—how do you identify those individuals carrying the schizophrenia genotype but not the overt, psychotic, dysfunctional phenotype? Until this can be done in an objective fashion, it will be very difficult to escape accusations of circular reasoning. We need to be able to assess genotype independently of the sorts of phenotypes which might be involved in producing differential fitness; thus we must develop nonbehavioral diagnostic tests that will identify those individuals who are coping, and presumably often thriving, despite the presence of a genotype which is so destructive in others.

The search for an easily determinable and reproducible marker in the body or bodily fluids of schizophrenics or their relatives has so far been a rather futile enterprise. Recently, Wong et al. [39], using PET scan images, have identified elevated dopamine receptor density in the brains of drug-naive schizophrenics. This is an important discovery, but the technique is not very useful if we hope to study schizophrenia in a broad evolutionary perspective. Localization of an actual genetic (chromosomal) marker, which has been accomplished at a preliminary level for

bipolar illness in one small population [40], has apparently not been achieved for schizophrenia. Larger-scale searches for carriers of the schizophrenia genotype will probably require diagnostic tests that measure a "schizophrenic response" rather than identify some endogenous marker. We see two possible tests that might be of some use in this regard.

The first of these "response" tests is based on the reasonably well-established increased sensitivity, using both psychological and physiological measures, of schizophrenics to amphetamines and other dopamine agonists ([41], but see also [42]). This increased sensitivity is, of course, not surprising, as it constitutes another piece of evidence supporting dopamine pathway involvement in the schizophrenic condition. It is well known that chronic amphetamine use in humans can lead to a psychosis virtually indistinguishable from paranoid schizophrenia. Individual humans are known to differ with respect to amphetamine sensitivity, and studies on identical twins have shown that amphetamine response is genetically influenced [43]. These clues, however, have apparently never been followed up with examinations of amphetamine response in the first-degree relatives of schizophrenics. We suggest that such studies have the potential of identifying those individuals who possess the schizophrenia genotype (and therefore, the biochemical difference leading to increased sensitivity to amphetamines) but who do not manifest the overt behavioral symptoms of schizophrenia. A study of this type, measuring the effects of LSD-25 on the relatives of schizophrenics, was carried out in 1962 by Anastasopoulos and Photiades [44]. They found that some normal relatives of schizophrenics exhibited "schizophrenic-like" intoxication symptoms; unfortunately, their investigation was hampered by a lack of definition of a normal response to LSD and by the sole reliance on qualitative, behavioral features as a means of distinguishing between normal and abnormal response.

The second proposed test depends on the existence, first reported in the early part of this century [45], and rediscovered in the early 1970s by Holzman and his colleagues [46], of eye tracking dysfunction (ETD) in schizophrenics. As Levin notes:

> Abnormal pursuit eye movements in schizophrenics consist of intrusive saccades which are present during any visually guided slow eye movements, and in some patients are related to nonvoluntary attention. Studies of potential artifacts show that the phenomenon is not due to medication, age, inattention, or poor motivation. [47, p. 37]

Numerous studies on ETD in schizophrenics have been carried out (see *Schizophrenia Bulletin* 9 for a review), and Holzman's group [46, 48–50] and others [51, 52] have published a number of genetic studies concerning schizophrenia and ETDs. A general conclusion is that "eye-tracking dysfunctions represent familial markers of vulnerability to schizophre-

nia" [49, p. 136]. ETDs appear in about 50–85 percent of diagnosed schizophrenics, depending on the study; and in 45 percent of their first-degree relatives. They also appear in about 40 percent of manic-depressives, but these "false positives" appear to be an artifact of lithium medication [53]. The first-degree relatives of manic-depressives, in contrast to the situation for schizophrenics, do not show increased levels of ETDs. Matthysse et al. [26] have provided a "quasi-Mendelian" genetic model for the transmission of schizophrenia and eye tracking dysfunction: schizophrenia and ETD are seen as the manifest traits, with differing probabilities of expression, of a single latent condition. They believe that the most useful current interpretation of the data is that this latent condition is determined by a single gene. Interesting studies by Siever et al. [54, 55], measuring eye tracking in large samples of normal and screened (for extreme scores on psychological and physiological tests) volunteers, have shown that poor eye tracking correlates with schizotypal personality and a psychologic profile characterized by social introversion. It is apparent that the two approaches outlined above, drug response and ETDs, used in combination, may well significantly increase the specificity of identification of the schizophrenia genotype.

Such a capability would, of course, be extremely useful for gaining insights into many aspects of the schizophrenia problem. Cross-cultural studies of schizophrenia, especially those that attempt to look at the condition in non-Western societies and cultures, are seriously handicapped by generalized diagnostic criteria often difficult to apply in social and cultural settings differing markedly from those in which the criteria were developed. Although Murphy [21] and others have demonstrated that this problem is not insurmountable, the development of nonbehavioral diagnostic criteria would certainly be of great use in overcoming the problem of cross-cultural indeterminacy. Of the two outlined above, ETDs would appear to be of greater current utility for such cross-cultural and interpopulational studies. Drug responses, while probably "closer" to the actual biochemical mechanisms involved in schizophrenia, have yet to be tested at the familial level, never mind the populational. In addition, they require a clinical setting for proper investigation, thus making large-scale population sampling unwieldly and costly. ETDs, on the other hand, have been studied extensively at the family level, and do not require clinical support. Large samples, as in [55], are readily obtainable.

Suppose, for the sake of argument, that the information content of these two approaches is substantially above background levels, and that they, individually or in combination, will identify most carriers of the schizophrenia genotype (pathological and "normal"). Where might such a capability lead us? What positive and negative consequences could such knowledge have? It seems to us that such questions have answers at

several levels. First, we consider the possibility of testing certain corollaries of the evolutionary hypothesis of schizophrenia detailed above. The most directly relevant of these would appear to be the implied positive correlation between the "complexity" of a society or culture (which we would define in terms of the number of different roles to be played within it) and the number of schizophrenics it allows. Thus schizophrenia appears to be a "condition/result/disease of civilization" (although we disagree with some of his conclusions, see Torrey [2] for a good review of the topic), and we would predict that the schizophrenia allele frequencies should be correlated with the length of time since the populations involved ceased a hunter-gatherer existence. As we have already noted, the potentially adaptive behavioral traits found in the relatives of schizophrenics (carriers) must be identified by extrapolation from the behavior of overt schizophrenics. We have identified two such traits as being potentially adaptive in certain types of social environments: asociality, primarily, with the occasional result of creativity. We expect a complex social environment to be more "fertile" than a simple one for the possessors of the schizophrenia genotype. Complex societies are, by definition, more variable than simple societies; hence they are more "tolerant" of behavioral variation. Note that this does not mean that such societies are in any sense more liberal or open-minded, but that the maintenance of variability is built into their structures. In addition, as pointed out by Hayek [56], complex societies are distinguished not only by a division of labor but also by a "fragmentation of knowledge." Such fragmentation allows individuals who lack general social skills but possess specialized knowledge and understanding in nonsocial realms, to survive within, and even benefit, their social group—and, of course, themselves. Social dysfunction may therefore be more tolerated in a complex rather than a simple society; this then may be a factor in the maintenance of the schizophrenia genotype in more complex societies.

We point out that a complex social environment will result both in "selection for" the schizophrenia genotype and "selection of" it, as well (sensu Sober [57]; see also Vrba and Gould [58]). Selection *of* schizophrenia will result because a complex environment will allow greater role variability—will allow those individuals who have taken back some of their individuality from the social group to survive and presumably thrive. Selection *for* schizophrenia, or more precisely for the relatives of schizophrenics, will also result on those rarer occasions when innovation, creativity if you will, is somehow rewarded. Increasing social complexity requires periods during which new social roles, structures, and relationships are created. It is apparent that complex societies need not actively encourage variability and innovation to be in some sense "schizophrenogenic." Of course, those that do will reap the benefits and suffer the consequences.

The eye tracking approach should be of use in studies that could directly or indirectly test the hypothesis outlined above. One of our goals is to determine whether or not differences in schizophrenia prevalence among various cultures or cultural subgroups has any biological component that might be identifiable by measurement of eye movements. Results from such a study could then be combined with cultural historical data to see how well they fitted the evolutionary hypothesis. The epidemiological literature, which of course is based on the overt phenotype regardless of underlying etiology, offers many populations in which such tests could be carried out. For example: (1) Taiwan—where aboriginal Taiwanese groups are found to have much lower rates of schizophrenia than those found in ethnic Chinese populations also living on the island [59]; (2) Hawaii—where those of Japanese and Chinese descent have the highest rates for schizophrenia, Filipinos intermediate, and Caucasians the lowest [60]; (3) United States—where attempts to determine rate differences in mental illness between blacks and whites have produced equivocal results and some controversy [61]; one study indicates that blacks may be systematically misdiagnosed as schizophrenic when the real condition is affective illness [62]; (4) Micronesia—where some island populations have no schizophrenia, presumably the results of genetic drift [10]; studies here would serve to test the eye movement method as a measure of populational variability.

The lower frequencies of schizophrenia seen in nonindustrial societies have led many investigators to the conclusion that such social configurations are somehow "better" for schizophrenics; that one reason there are apparently fewer of them is that they are less often "driven" to need medical attention. This is, of course, counter to the theory outlined above: we believe that more complex societies, in that they provide a plurality of possible roles, select for, to a limited degree, a schizophrenia genotype and are therefore "better" for those possessing that genotype. There is a substantial body of data indicating that the prognosis of schizophrenia is much better (lower rates of rehospitalization after an initial episode, e.g.) in nonindustrial than in industrial societies; therefore, even if overall prevalence between industrial and nonindustrial cultures were similar, the industrial society would have many more chronic schizophrenics [63]. This has led "social labeling" theorists ([64, 65]; but see [21]) to suggest that "the less affected European patient may be 'trapped' within an established sick-role by the superficial rationality of his society's view of this sickness" [66]. An alternative explanation suggested by the evolutionary hypothesis outlined above is that the "less affected" individuals in complex societies (that is, the "normal" relatives of overt schizophrenics) are doing quite well; while it is the "less affected" individuals in simpler societies that come to the attention of Western medicine, albeit for a relatively short period. The higher abso-

lute and relative numbers of chronic schizophrenics in complex societies are therefore seen to be the result of a higher frequency of the schizophrenia allele(s), coupled with the likelihood that those less affected carriers of the allele(s) will more readily find a useful role somewhere in such societies. As with so many hypotheses concerning the cross-cultural distribution of the schizophrenic condition, this one can only begin to be tested when we have some idea of the cross-cultural distribution of the schizophrenia genotype.

Risk and Marker Studies

Anyone who seriously suggests, as we do here, that we ought to determine the underlying frequency of the schizophrenia genotype in human populations, via marker studies in a cross-cultural, evolutionary perspective, should for a moment at least consider the potentially negative consequences of such studies. Such a potential may be expressed at two levels, the individual and the populational.

At the individual level, any worthwhile survey will find subjects who are in possession of the marker and may then be considered "at risk" for the condition under study. In the schizophrenia case, this might be particularly troublesome, given how little we know about the way biochemistry and environment combine to produce the overt condition. Labeling at this level may raise the risk of a "self-fulfilling prophecy" developing—for example, that an individual, knowing of his condition, might use such knowledge as an excuse to give up in areas where he might be having difficulty. The other side of such a concern is that such knowledge would allow other individuals to develop an increased understanding of themselves, and of their strengths and weaknesses. The nature of the general balance here was, of course, recognized long ago, and is perhaps best exemplified by the inscription "know thyself" over the portals of Delphi. It should, of course, be the right of an individual, should he choose so, to know the results of any susceptibility test. Of greater concern is how others will deal with such information. Should the day come when we can identify schizophrenia carriers with some degree of accuracy, we suggest that the question of what to do with such information be approached with great care; for the goal is to decrease the negative aspects of the condition without also doing away with the positive—and we again emphasize that, from the evolutionary perspective, the positives must at least balance the negatives. Until the population as a whole becomes much better conditioned to the idea of meaningful human diversity in the area of mind, knowledge of an individual's carrier status had best remain with the individual.

In studies of the frequency of the schizophrenia genotype in different

populations, we should be careful to avoid the errors of the psychologically oriented cultural anthropologists of the 1930s and 1940s—for example, Benedict [67], who sometimes used psychopathological terminology to characterize entire cultures. Populations most at risk here are probably subcultures subsumed within more dominant cultures. Knowledge of relative frequencies of the schizophrenia genotype could fuel speculation that one culture is "more mentally ill" than another and provide justification for preexisting prejudices. Or, on the other hand, some cultures with lower frequencies of the schizophrenia genotype may be perceived as therefore lacking innovative or creative individuals. We stress that our hypothesis is an explanation not of creativity or innovation or asociality but of schizophrenia; arguments going in the "opposite direction" are of an entirely different kind. Despite the potential dangers of the studies discussed above, we can only go with the general ethic of continuous striving for greater understanding, with the implicit assumption that this is always a net plus. The alternative, of course, allows for far greater evils. Clearly the notion that ignorance is bliss runs counter to the whole reason for the existence and development of the human lineage over the last 2 million years.

Conclusion

In this paper, our concern has been less with the relatively rare overt, psychotic, and dysfunctional schizophrenic than with those nonovert carriers of the schizophrenia genotype responsible for the maintenance of the condition in human populations. Schizophrenia is not an aspect of human nature that we should seek to simply overcome or rise above; understanding the condition should allow us to take advantage of it at both the group and individual levels. Understanding will certainly be facilitated by success in identifying functional, nonpsychotic carriers of the schizophrenia genotype(s); in coming to see how they have learned to, at worst, cope with, and at best, take advantage of, their condition; and in gaining a better sense of the evolutionary history involved through cross-cultural studies. We feel justified in strongly suspecting that our population is divided into a very large majority of individuals who do not possess the schizophrenic genotype(s), and a small minority (perhaps 5 percent) who do. We also feel justified in strongly suspecting that individuals in the two groups may well perceive, and react to, themselves and the rest of the world in meaningfully different ways because of these genotypic differences. The major current problem is that people are not at all comfortable with the idea of significant interindividual and, in particular, intergroup differences in mind. Yet this is precisely the nature of the condition leading to, in a minority of its possessors,

what we have come to know as schizophrenia: there is a group difference in mind. The condition *must* be a net selective plus, and this evolutionary understanding is, at present, totally unappreciated.

The possessors of the schizophrenia genotype(s) need to be made aware of the fact that their perception and understanding of particular situations may differ from those of the vast majority of the population because their minds are in fact different; that they may have greater difficulties in initiating and maintaining social relationships because they are inherently less social and less socially adept; and, especially, that there is no one, or no thing, out there making them this way. They must come to see that the difference is inside them. And the earlier they come to see and accept this, the greater the chance that they will be able to come to grips with, and, it is hoped, take advantage of their increased understanding of themselves. We emphasize here that all of this is perfectly possible today and is in no way dependent on having identified them individually. Education is necessary to make known the fact that schizophrenia is a historically important aspect of human biological variability with major current individual and social implications.

The vast majority then needs to be sensitized to the existence of a small minority whose individuals are in fact different in mind—and the critical aspect of this sensitization process will be to explain how it is that one can be so different and still advantaged, especially when confronted with the all-too-obvious examples of noncoping possessors of the same condition. This will not be an easy task, but it is one that must be undertaken. Otherwise we leave both groups in ignorance of the realities of their existences and of the evolutionary history of how and why those existences came to be. That history is intimately and profoundly involved with the essence of being human and may come to serve as an exemplar for many other aspects of the necessary variability of brain and mind in a species where the adaptation and evolution of brain and mind have been, in large part, the adaptation and evolution of the species itself.

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