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SCHIZOPHRENIA EPIGENESIS?

ABSTRACT. I begin by examining how genetics drives schizophrenia research, and raise both familiar and relatively novel criticisms of the evidence putatively supporting the genetic basis of schizophrenia. In particular, I call attention to a set of concerns about the effects of placentation on concordance rates of schizophrenia in monozygotic twins, which further weakens the case for schizophrenia's so-called strong genetic component. I then underscore two critical points. First, I emphasize the importance of taking seriously considerations about the complexity of both ontogenesis and the development of hereditary diseases. The recognition of developmental constraints and supports is crucial, for attention to development exposes the naivete of too many models of gene action in the aetiology of disease. Secondly, I attend to those schizophreniologists who ignore methodological criticisms and thus presume a genetic basis for schizophrenia, and then seek the 'schizophrenic genotype' lacking an adequate phenotype. In response I attempt to demonstrate the necessity of a sustained effort at characterizing the phenotype of schizophrenia as an enabling condition for the whole enterprise of psychiatric genetics – and for psychiatry itself. Without the organism-level phenotype, research at the level of genes will remain unproductive – assuming of course that research at the genetic level is appropriate at all.

KEY WORDS: aetiology, complexity, development, developmental systems, epigenesis, phenotype, placentation, psychiatric genetics, schizophrenia

INTRODUCTION

A principal investigator in the Danish adoption studies, Seymour Kety, enthusiastically proclaimed 25 years ago that "if schizophrenia is a myth, it is a myth with a strong genetic component!" [1]. Since then, a number of critics have convincingly argued that the evidence for the genetics of schizophrenia is equivocal at best [2–5]. Nevertheless, research into molecular aspects of schizophrenia continues unfettered, motivated by a positive assessment of the classic twin and adoption studies.¹ Just why is that? A likely explanation for the proliferation of molecular research into schizophrenia – despite the fact that this research has thus far proven unsuccessful, and despite the further fact that the classical basis on which it rests is profoundly unstable – is that some schizophreniologists work with an unfortunate understanding of ontogenesis, one which unjustifiably



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privileges genes as necessarily aetiologically foundational. In this article I perform three tasks: (1) I raise both familiar and relatively novel criticisms of the evidence for the genetic basis of schizophrenia; (2) I critically interrogate the gene-centered model of ontogenesis employed in schizophrenia research, and sketch an alternative; and (3) I urge the redirection of schizophreniology away from genetic aetiologies and toward the more fundamental concern of elucidating the phenotype of schizophrenia.

THE HEREDITARY BASIS OF SCHIZOPHRENIA

“The genetic contribution to schizophrenia is the most clearly established etiologic factor. Sadly, this seemingly impressive statement is simply another way of admitting that we know disturbingly little about the causes of schizophrenia” [7]. The reasons are quite clear: while classical studies have contributed to the conviction that there is indeed a genetic influence on the development of schizophrenia [8–10],² these studies are problematic in a variety of ways. Further, family, twin, and adoption studies do not indicate which specific genes are culpable, and molecular geneticists have failed in their efforts to link genes with the illness. Further still, it is clear that schizophrenia does not follow any Mendelian pattern of inheritance. So while schizophrenia – like catholicism – seems to run in families, that appears to be virtually all we know about the aetiology of the illness.

I will not dwell on the details of the family studies primarily because familiarity – as established through the family studies – implies either a genetic theory, a nongenetic biological theory, an environmental theory, or (more plausibly) some hybrid epigenetic theory: familiarity does not by itself imply a genetic basis for schizophrenia.

Genes are thought to be implicated more directly by the twin study approach. The method is straightforward. Identical twins derive from a single zygote; they are thus monozygotic (MZ) and share identical genes. Fraternal twins are dizygotic (DZ), sharing less than 100% of their genes (as do other full siblings). Given the raw genetic make-up of twins, we would expect MZ twins to be more concordant for a genetically determined trait than we would DZ twins. An immediate problem arises, however, for it is enormously difficult in practice to abstract the *genetic* identity of MZ twins from their nearly identical *physical* appearance; the result is that throughout their lives many MZ twins have very likely been treated in exactly the same way by exactly the same people; some even ape each other, perhaps in an effort to confound those who would tell them apart. Consequently, in addition to sharing genes, MZ twins share environments. That they may be more concordant for a given trait might just as easily

be the result of their environmental similarity rather than the result of their genes. Twin researchers brush off these and other methodological difficulties, and conclude that as MZ twins are more concordant for schizophrenia than are DZ twins, or any other relatives, then schizophrenia has a genetic basis.³

Various twin investigators have used various criteria in diagnosing their probands and co-twins; some studies have used a pairwise concordance, other have used a probandwise concordance;⁴ some studies have only a small number of index cases while other studies are massive by comparison; and some investigators provide inadequate case details, especially regarding the determination of zygosity in the twins. The result is that different literature surveys and commentaries deem different studies methodologically sound (or merely adequate, acceptable, and so on) and hence provide (sometimes very) different average concordance rates for MZ and DZ twins.

Gottesman [14] drawing on data from Gottesman and Shields [8], arrives at a concordance rate of 48% for MZ twins and 17% for DZ twins (we can presume Gottesman is using the probandwise method). Kringlen [15] bases his average concordance rates on only the register-based studies from the Nordic countries. He reports 30% MZ and 10% DZ (pairwise) and 40% MZ and 15% DZ (probandwise) concordance rates. Torrey [16], a sometime collaborator of Gottesman's, has a few more reservations than does Gottesman. Torrey is concerned to consider the concordance rates produced by only those studies [17–24] which employed representative samples and in which zygosity was reliably determined. He arrives at pairwise concordance rates of 28% for MZ twins and 6% for DZ twins.

But these various rates may inflate the differences between MZ and DZ concordance. A recent hypothesis suggests that twin studies may have misled investigators into inferring a genetic basis of disease [25]. We tend to assume that MZ twins share both an identical prenatal and identical postnatal and childhood environment, while DZ twins share similar (but not identical) prenatal and postnatal environments – but this assumption is inaccurate in a number of respects. Consider that dizygotic twins are the result of the fertilization of two ova; further, each twin-embryo develops within the confines of its own set of fetal membranes. DZ twins are thus dichorionic (DC). But while MZ twins develop from a single zygote, they do not necessarily share the same set of fetal membranes; that is, MZs might be monochorionic (MC) or they might be DC. When twinning occurs at an early stage (usually during the first 4 days after fertilization), the resulting MZs will be dichorionic (DC-MZ) and *in this respect will resemble DZ twins and not MZ-MC twins*. Their fetal circulation will

almost never be connected. Approximately 33–40% of all MZs are DC. The rest of the MZ twins will be monozygotic. That is, they will share the same chorionic membrane and placenta, and occasionally a single amnion. In about 90% of these MC-MZs, fetal circulation is shared [25, 26].

This point about shared fetal circulation, chorion, and placenta is crucial: MC-MZ twins share a more similar prenatal environment than do DC-MZ twins; MC-MZs are, for instance, more likely to share infections than are DC-MZ twins. Should MC-MZ twins be more concordant for schizophrenia than DC-MZs, then one explanation would not invoke a genetic aetiology at all: instead, a mother's exposure to infectious disease might increase the risk of later schizophrenia in her children [26].⁵

Davis and Phelps [26] outline a very complex strategy for retrospectively determining placentation status. They err on the side of conservatism to avoid inflating their results. They determine that 60% of MC-MZs are concordant for schizophrenia, compared with 32% of DC-MZs. In a further study with another colleague [31], they refine the process of determining the placentation status, with nearly identical results. They thus conclude that it is very likely that the subset of MC-MZ twins inflates the MZ concordance rates in twin studies.

To summarize concordance according to the twin studies: Kallmann reported long ago an MZ concordance rate for schizophrenia of 86%, compared with 15% for DZ twins [32]. In 1991, Walker et al. reported on a meta-analysis of 21 studies: they found pairwise concordance rates of 25% (MZ) and 7% (DZ) [33]. Now we find, through Davis et al. [26, 31] that even this drop of 61 points in MZ concordance and 8 points in DZ concordance (and so 53 points in the difference between MZ and DZ concordance rates) may not be enough if it is the case that MC-MZ twins artificially inflate MZ concordance. The twin-study evidence for a genetic basis for schizophrenia is thinning indeed.

I will briefly note one further problem with inferring a genetic aetiology for schizophrenia on the basis of twin-studies. Rose et al. [2] indicate that though DZ twins experience environments less similar than those that MZ twins experience, we would nonetheless expect DZ twins to experience more similar environments – both *in utero* and in the world – than ordinary siblings. The upshot is that “from an environmental [nongenetic] viewpoint – and only from such a viewpoint – we would expect concordance among DZs to be higher than among ordinary sibs.” As it turns out, this is indeed the case: DZ twins are more concordant for schizophrenia than are ordinary siblings; and so it would be eminently plausible to infer that the still higher concordance of monozygotic twins ought to be attributed not to genes but rather to their even greater environmental similarity [2].

That twin investigators ignore these sorts of difficulties is evidence of a *gene-centric approach*, whereby any difference in MZ-DZ concordance is immediately explained by invoking genes.

This gene-centrism is further bolstered by the adoption studies, which Gottesman and Shields refer to as “the straw that broke the environmentalist’s back” [cited in 5]. Solomon Snyder called the first adoption studies “the best work that’s been done” in biological psychiatry. “They take out all the artifacts in the nature vs. nurture argument” [cited in 2]. Yet these studies are themselves not significantly less problematic than any of the other classical studies. There are three types of adoption studies. First, there are studies examining the biological and adoptive relatives of adoptees serving as schizophrenic index cases. Secondly, there are studies examining the offspring of schizophrenic biological parents who serve as index cases. Thirdly, there are so-called cross-fostering studies, in which the biological parents are not schizophrenic, but whose child has inadvertently been placed with an adoptive parent who is later diagnosed as schizophrenic.

Rose et al. [2] describe the details of a study of the first type, that of Kety et al. carried out in Denmark [34]. The Danish Adoption Studies (DAS) are standardly thought to provide definitive evidence of the biological heredity of schizophrenia [3]. With 34 schizophrenic adoptees as index cases and 34 control adoptees with – in Gottesman’s words [12] – “clean pedigrees,” Kety et al. traced 150 biological relatives of the index cases and 156 biological relatives of the controls. Rose et al. indicate numerous methodological problems with this study, primary among them the paucity of straightforwardly diagnosable *schizophrenics* among the relatives of either the index cases or the control cases. There was, it seems, exactly “one chronic schizophrenic among the index relatives and one among the controls” [2].

So Kety et al. formulated a (not necessarily *ad hoc*) ‘schizophrenic spectrum of disorders’ comprising numerous illnesses (including chronic schizophrenia, borderline state, inadequate personality, uncertain schizophrenia, uncertain borderline schizophrenia, and uncertain borderline state). Even then, the authors found nine index cases with at least one schizophrenia spectrum diagnosis among their biological relatives, compared to only two such control cases. As Rose et al. remark skeptically: “That difference is the supposed evidence for the genetic basis of schizophrenia” – without the schizophrenia spectrum, Kety et al.’s study would have revealed no important genetic influence [2]. Moreover, in their 1975 study, Kety et al. [35] excluded the diagnosis of ‘inadequate personality’ from the schizophrenia spectrum, presumably because it was

diagnosed equally frequently in index and control groups [2, 3]. But had the 1968 definition of the schizophrenia spectrum omitted the diagnosis of ‘inadequate personality,’ then the 1968 results would have failed to be significant [3].

An additional difficulty with the adoption studies is ambiguity as to whether interviews were conducted with living subjects, or were rather reconstructions from the hospital records of dead relatives [2, 3]. Consider an example discussed by both Rose et al. [2] and Marshall [3], that of a subject diagnosed with ‘inadequate personality’ in the 1968 study [34]; since that diagnosis falls within the boundaries of the 1968 definition of the schizophrenia spectrum, this subject contributed to the conclusion that schizophrenia has a genetic aetiology. This same subject was re-diagnosed for the purposes of the 1975 study [35] with ‘uncertain borderline schizophrenia’ – that is, she no longer had an ‘inadequate personality’ (a diagnosis which was by 1975 no longer part of the schizophrenia spectrum), but rather was re-diagnosed with a within-the-spectrum disorder, and thus continued to help demonstrate the genetic basis of schizophrenia. But as Rose et al. discovered, this subject, having committed suicide, was in fact never interviewed by the DAS investigators; rather, her two different diagnoses in 1968 and 1975 were reconstructed from hospital records – which indicated that she had actually been diagnosed by hospital physicians with manic depression! Rose et al. [2], astonished by their discovery, remark that “we can only marvel at the fact that the American diagnosticians, analyzing abstracts of these same records, were twice able to detect – without ever seeing her – that she really belonged within the shifting boundaries of the spectrum.”

Having considered in detail these and other difficulties with the various adoption-study methodologies, Rose et al. conclude that the weaknesses of the DAS are striking indeed, and wonder how such deep problems could have escaped the notice of those – like Snyder or Gottesman and Shields, cited above – who celebrate the adoption studies as removing all the artifacts that plagued earlier twin and family studies of behavior. A French meta-analysis reaches a similar conclusion [3, 36]: Cassou et al. set out to examine the scientific evidence for a genetic effect in schizophrenia. The ten reviews they selected for investigation declared unequivocally that the significance of genetic factors had been established. Yet after a meticulous and exhaustive analysis of each of the references in each of the ten literature reviews, the authors conclude that there is *no evidence for a genetic effect in schizophrenia*. Such a conclusion may be exaggerated, for the reasons to be examined below – but the study by Cassou et al. serves as an important counterpoint to the enormous enthusiasm expressed

by Kety (as quoted in the opening paragraph of this section) and many other schizophreniologists. This much is certain: the truth lies somewhere between these two extremes – which, of course, is to say that we still know too little about the origins of schizophrenia.

EPIGENESIS AND SCHIZOPHRENIA

Despite the difficulties schizophreniologists are convinced somehow of the genetic basis of schizophrenia. A good instance is Gottesman's conclusion that, upon review of the classical studies taken together, familiarity is due largely to shared genes rather than to shared environments (pre- and postnatal). We have, Gottesman claims, "cumulative credible evidence" for "a large, rather specific, and important genetic factor(s), in conjunction with putative, unspecified nongenetic factors in most cases, lead[ing] to the development, over varying lengths of time, of varying severities of schizophrenia(s)" [12]. Gottesman surely overstates his case. He has no idea of the relation between genes and what might be called the schizophrenia spectrum; this is the reason he parenthetically pluralizes both "factor" and "schizophrenia" itself. Furthermore, his choice of language is particularly telling. Along with others convinced of the value of behavioral genetics, despite a wealth of criticism, Gottesman pretends that the evidence from the family, twin, and adoption studies is methodologically adequate and that it consistently, though perhaps indirectly, points to a major genetic influence in the aetiology of schizophrenia. The hereditary basis of psychiatric genetics is, thus, invoked by fiat rather than deduced from solid evidence.

The doctrine of gene centrism to which I have alluded is the *a priori* endorsement of the preeminent role of genes in every aspect of human being. Gottesman and others demonstrate singular determination in their quest for the gene (or genes) as determinant of schizophrenia. In order to convince those skeptical about our knowledge of schizophrenia, these gene centrists are seeking a schizophrenic genotype which will answer all doubters. For psychiatrists have grown weary of defending their discipline – in particular, they are tired of responding to critiques that mental illness is not "real" illness (and thus that psychiatry is not real medicine). Schizophrenia is one of the most contested of psychiatric diagnoses, both within and without psychiatry; this fact has left schizophrenia researchers emboldened and embittered, and of the mindset that if they could simply identify a 'gene for' schizophrenia, then they would silence the skeptics once and for all.⁶ The idea is that a subfield of psychiatric genetics would raise the prestige of psychiatry as a medical specialty [37].

Of course, psychiatric geneticists are fully cognizant of the poverty of strictly genetic accounts of schizophrenia, and none proposes that a single gene of major effect, acting in virtual isolation, causes the disorder [38, e.g.]. Gottesman himself remarks that a genetic diathesis-environmental stressor approach is accepted by a majority of schizophrenia researchers, and that this sort of “interactionist stance” (Gottesman’s phrase) was already institutionalized by 1967 [12].⁷ Yet as Susan Oyama [39] has asked of the nature-nurture debates as a whole: if we are all interactionists, then what’s the problem? As she and others have observed, the trouble is with the very slipperiness of the concept of ‘interaction’ as such.⁸ For instance, interaction may occur at both populational (analysis of variance) and individual-developmental (analysis of causes) levels. In terms of populations, the task is to explain differences in traits in a population; that is, to account for phenotypic variation in terms of environmental variation, genetic variation, or both. From this perspective, interaction may be understood in two ways, additively (genes + environment = phenotype) or nonadditively (genes \times environment = phenotype). (Additivity in this context refers to the aggregation of independent influences – the contribution of the genotype is insensitive to any environmental factor, and the contribution of the environment is not influenced by the genotype [40, 41].) There is a longstanding dispute between those who downplay nonadditive interaction and emphasize additivity, and those who recognize significant nonadditive interaction.

The situation is equally charged in the context of individual development, where the task is to explain the source not of differences in traits but rather of the traits themselves. It is thus the effort to understand the causal activities of genes and environments in the ontogenesis of a trait. A significant source of disagreement in this domain involves conceptual slippage from the level of populations to the level of individual organisms. Though there is an obvious difference between understanding statistical variance-in-traits and understanding ontological causes-of-traits, we sometimes confuse the two and partition traits into genetic and nongenetic components just as we partition variation into genetic and environmental influences. That is a mistake, according to some interactionists, while it is perfectly acceptable to others. Does ontogenetic interactionism therefore refer to a thesis about genes (primary) and environments (secondary) as relatively independent factors, whereby genes are environmentally activated to produce the phenotype from what is thought to be ‘latent in the genotype’? Or rather is ontogenetic interactionism somehow more complex, consisting in a broader range of comparably important inherited and noninherited factors (DNA, cytoplasmic characters, nutrients, and more),

characterized by their context sensitivity (e.g., to temperature), developmental history, and spatiotemporal positioning in the cell and in the organism, interacting in interdependent ways in the constitution of the phenotype (which is not in fact presupposed in the genotype)? On the former account, interaction amounts to ontogenetically specific-information-bearing genes being expressed as a result of (usually nonspecific) nongenetic triggering; genes are primary, requiring but activation for ontogenesis to take place, and the phenotype is only a proxy for the foundational genes. On the latter account, the developmentally specific information resides not in the genes but rather in the spatiotemporally delimited developing system, which is therefore the ontogenetically primary unit; accordingly, interaction is not limited to gene-activation but rather implicates positive and negative feedback loops at a variety of levels within and without the developing organism which contribute to the very constitution of the organism [39]. Note that there is a qualitative difference between these two alternatives: the latter is not a more detailed presentation of what is implicit in the former, but rather a rejection of its basic premise of gene-centrism and its ostensible oversimplification of the nature of interaction.

This is all very abstract, to be sure, and it is therefore important to consider an example. For the remainder of this section, I will briefly criticize the first interpretation of population-level interaction, and then articulate a defence of the second interpretation of interaction at the level of individual ontogenesis, against the current of much research in schizophrenia genetics.

The following challenge to quantitative genetic efforts to disentangle the relative effects of genes and environments is many decades old. The central model employed by human behavioral geneticists assumes that hereditary factors are of necessity genetic factors, and presumes further that genes and environments act separately and additively, so that their respective contributions to a trait can be separated statistically [40]. The standard tools of statistical and population-genetic analyses either assume additivity, or do not detect nonadditive interaction and therefore presume that it does not exist. But it has been repeatedly shown that the statistical analysis of variance (ANOVA) does not detect nonadditive interaction not because it is not there, but rather because the test is insensitive [40, 42–48]. Thus, the presumption of additivity is misguided; meanwhile, research on large populations of different strains of laboratory animals has demonstrated that nonadditive interaction is the rule rather than the exception [summarized in 40].⁹

Nevertheless, the presumption of additive interactions prevails in psychiatric genetic research, and has contributed a sense of urgency to

efforts to decompose mental illness into individual genetic and environmental components. The problem is attributable in part to the neglect of developmental biology in the Modern Synthesis [40, 49]. Aetiological models of schizophrenia, motivated by population-level measurements of heredity that are specifically insensitive to gene-environment interaction, reduce the interaction of genes and environment to the (secondary) environmental stimulation of (foundational) predisposing genes. Consider the diathesis-stressor model upon which many schizophreniologists base their aetiological understanding of schizophrenia. In a standard diathesis-stressor model, *diathesis* denotes a predisposition while *stressor* refers to the event(s) which trigger(s) the schizophrenic episode. What counts as a stressor might be a single event or a series of them, and the stressor(s) must be understood in context. It is accurate to characterize a diathesis-stressor model as a genes-*plus* model of schizophrenia, for it ‘adds-on’ environmental influences (as stressors) to the underlying (genetic) predisposing substrate [50].

Gottesman refers to such a model as an ‘epigenetic’ account of schizophrenia. It is unclear what exactly Gottesman means by this plastic term which has so many interpretations in contemporary and historical biological literature, but it is possible to surmise Gottesman’s sense. The term ‘epigenesis’ dates back at least to William Harvey writing in 1601, but Aristotle is often referred to as the first epigenecist [51]. The basic idea of epigenesis, especially as elucidated in the seventeenth century, is that the traits of organisms are not preformed *in utero*, but rather that novelty emerges during the developmental process. C.H. Waddington updated the concept of epigenesis for the twentieth century with his notion of ‘epigenetics’ as developed beginning in the 1940s. For Waddington, ‘epigenetics’ is a combination of the classical notion of epigenesis with the study of genetics (both classical and, later, molecular) [52–54]. A common modern definition which persists in this vein is that ‘epigenetics’ “refers to the multiple genetic and nongenetic factors that influence or regulate gene activity during development” [55]. A plausible conjecture, then, is that for Gottesman the schizophrenic is not preformed, not curled up in the zygote, but rather the predisposition for schizophrenia exists preformed in the genes from conception, and emerges epigenetically under the ‘right’ developmental conditions.

On this account of epigenetics, the primary emphasis is on the ‘genetics,’ not the ‘epi,’ and epigenetic control takes the genotype as its starting point and the phenotype as its endpoint [55].

But as implied by the second of the two versions of interactionism, there are ways of interpreting ‘epigenetics’ and ‘epigenesis’ (and the epigenesis

of schizophrenia) without recourse to the causal, methodological, or ontological primacy of the genes. For instance, unlike Gottesman, Waddington was not a gene-centrist. Surely genes were important to Waddington, but only as part of a complex developing organism not reducible to its genes [56, 57]. That is, it is possible to assess the ‘epi’ as just as important and worthy of analytical attention as the ‘genetics,’ of epigenetics. From this point of view, the appropriate domain of epigenetics is not the space between genotype and phenotype, but rather that between egg and developing organism, in sociocultural context. On such an account, epigenetic processes are therefore coextensive with ontogenesis as a whole, and not merely with gene activation. Furthermore, note the corollary: ‘heredity’ cannot be reduced to genes alone, for we inherit much more than a genome at conception. Accordingly, to interpret the classical studies of schizophrenia as supporting not merely that schizophrenia runs in families, but that it is thus a genetic disorder, is to step unwisely.

Such an alternative position has been advanced by proponents of developmental systems theory (DST) [39, 49, 58–62]. According to DST, the secondary epigenetic triggering of an encoded, inherited genetic predisposition misconstrues organismic development altogether. Genes-plus theories make the mistake of relegating developmental processes and life experiences to the role of expressing, translating, or otherwise mediating the underlying, preestablished genetic programme. This idea that phenotypes are transmitted through coded instruction sets is misguided, according to DST, for phenotypes are not transmitted at all but rather “constructed anew” in each individual life-cycle through strong organism-environment interactions throughout development. The basic unit of development is not the epigenetically regulated genetic program, but rather the organism-in-an-environment system whose various multileveled components interact nonadditively over time in the production of the mature organism [62].

For adherents to DST, development is, therefore, not genes-plus anything; it is strongly interactive, not additive. Schizophrenia, like any other trait, complex or simple, is not unleashed, but is rather “constructed epigenetically through ontogeny” [59]. Genes are surely a relevant factor in schizophrenia – as in most human characters – but they simply are not primary, not foundational, not fundamental. In lieu of the notion of environmental triggering of genetic potential inherent in gene-centric epigenesis, commentators such as Oyama [58] insist that development ought to be thought of as “a contingent series of constructive interactions, transformations, and emergences” not reducible to preformed informational genes and their epigenetically mediated products.

Eva Neumann-Held's recent criticism of standard concepts of the gene [61] foregrounds many of the concerns of DST. In particular, she underscores that the meaning and function of a given gene are necessarily context-dependent, dependent that is on a variety of ontogenetic processes in the developing organism. But Neumann-Held takes the additional step of arguing that the *structure* of a gene is itself irreducibly context-dependent, subject to and so constitutively contingent on a wide variety of contextual factors in development. "Independently of context and system, the DNA has neither structure, nor function, nor program, nor information" [61; see also 62]. The focus on genes as preformed determinants – even as parts of complex networks of genetic and nongenetic partial determinants – is therefore misguided. Genes do not exist in isolation – there is no such thing as a genome without a system; neither are genes somehow prior to the developing organism, awaiting epigenetic activation. The implication of developmental systems theory, especially as elaborated by Neumann-Held, is that the very idea of genes-plus-anything is a mistake.

Gottesman acknowledges the validity of certain crucial elements of the DST account, for instance that "gene expression is always environmentally mediated" [64]. To his credit, at no point does Gottesman fail to recognize that behavioral phenotypes are necessarily produced by both genes and environments – the basic presumption of all forms of interactionism. In fact, Gottesman calls this a "truism" [64]. But, I contend, he does not take seriously the limitation that it imposes on behavior genetics, namely, that, as Gray notes, "it is not possible to assign causal primacy nor to dichotomise developmental causation into internal and external components" [59; also, e.g., 48, 46, 65–68].

Gottesman's most recent proposal is to underscore that "there may be *partially* genetically influenced *predispositions* for basic behavioral tendencies, that under certain experiential contexts, make the *probability* of developing psychopathology higher for individuals who possess greater rather than lesser degrees of such behavioral tendencies" [64; italics in the original]. But if that is all that psychiatric genetics can tell us, then its medico-scientific import is ambiguous at best, and Gottesman's middle-way is something of a dead end. For virtually all of the characters of organisms are indeed genetically influenced; no one doubts this; it is unclear, therefore, what practical or therapeutic end is served by focusing on genes and not the complex behaviors or behavioral processes themselves (except that, thanks to funding decisions and the particular interests of geneticists, the genes may be more experimentally tractable [70–72]). Meanwhile, many of Gottesman's colleagues are not likely to admit (and

even less likely to take seriously) the limitations of genetic explanations of behavior.

Consider, for instance, the recent, representative remarks of Anne Farmer and Michael Owen [73]:

The Human Genome Project is the enabling technology by which the genes contributing to the genetic aetiology of common familial disorders, including the major psychiatric disorders, will be identified. We may be uncertain precisely how quickly and by what means such discoveries will be made [74] but there is little doubt that they will happen and that the knowledge gained will radically alter clinical practice. . . . The accuracy of diagnosis of major psychiatric disorders will be greatly enhanced and the complex interplay between environment and genotype will be increasingly understood.

Such faith in the promise of the Human Genome Project (HGP) is commonplace among psychiatric geneticists.¹⁰ But if we take seriously the challenge of developmental systems theory, then we must recognize just how far removed the HGP's official human genome is from the actual complexity of interactive, spatiotemporally delimited, context-dependent developmental processes in organisms which in fact co-determine both the structure and function of genes [61]. "Developmental information is not *in* the genes, nor is it *in* the environment, but rather it develops in the fluid, contingent *relation* between the two" [59].¹¹ It is by no means obvious therefore how the production of a one-dimensional readout of As, Cs, Ts, and Gs – frozen in time, abstracted from developmental context – will significantly improve our understanding of ontogeny, or of the aetiology of disease [78].

REORIENTING SCHIZOPHRENIOLGY

Of course, mapping and sequencing the genome are not the only ways to search for genes implicated in the aetiology of a disease. Another molecular genetic technique used in schizophrenia research is the linkage study, which searches for disease genes of major effect shared by a number of affected members of a family. Linkage suggests that the genetic marker and the disease gene are relatively close together on a chromosome; if so, then, in violation of Mendel's Law of independent assortment, they are likely to be inherited together; "if this is the case the marker and the disease will be found together in family members more frequently than would be expected by chance" [10]. Two types of linkage studies are those premised on the roughly 30 or 40 classical genetic markers (e.g., blood group antigens, human leukocyte antigens), and those exemplary of the new genetics, premised on the techniques of recombinant DNA. These newer techniques have allowed for the introduction of a massive number of

markers consisting in, for instance, DNA fragments known as restriction fragment length polymorphisms. If a marker is shared between affected family members, additional and increasingly sophisticated tests may allow the gene itself to be identified [10, 79–80].

That genes are the corner pieces of the aetiological “puzzle of schizophrenia” [81] is self-evident to any number of schizophrenia researchers, as well as to geneticists, physicians, and lay people [82, e.g.]; and so schizophreniologists have sought to identify linkage between particular chromosomal loci and aspects of the schizophrenic phenotype. The researchers operate under the presumption that replicated genetic linkage studies “will shed enormous light on the genetic aspects of mental illness, because they will turn the circumstantial evidence of genetic involvement gained from population genetic strategies into hard, physical evidence” [12]. Unfortunately, molecular geneticists have yielded no results that have been replicated ascribing to specific genes particular roles in the development of schizophrenia [83–85]. Some researchers are astonished by these failures: “surprisingly, despite decades of epidemiologic research pointing to genes as an etiologic mechanism for schizophrenia, application of the sophisticated methods of molecular and statistical genetics that are now available has not revealed which genes are involved and how gene products lead to the disorder” [81]. But, as I will show, this result is in fact not surprising at all.

It is important to understand that the techniques for analyzing linkage are indeed impressive and powerful, but only under specific conditions. Cardno and McGuffin [10] indicate that three major assumptions underlie the genetic-linkage method:

[First,] that a gene of major effect exists; secondly, that only one disease gene is segregating in a given family (i.e. there is homogeneity); and thirdly, that the mode of inheritance is approximately known. In studies of schizophrenia none of these assumptions is completely met at present.

The authors could not have further understated this last remark. First, every model enjoying currency among schizophrenia researchers is some variation on a polygenic approach [83]; secondly, the heterogeneity of schizophrenia is perhaps the most widely agreed-upon aspect of the construct [86, e.g.], while the fallout of Kety et al.’s 1968 study is that affected biological relatives of adopted schizophrenics will be beset mainly not by schizophrenia but rather by schizophrenia-*spectrum* diagnoses; and thirdly, we have virtually no clue as to the mode of transmission or inheritance of schizophrenia [83].

In addition to fulfilling the requirements of these three assumptions, the illnesses for which linkage studies have successfully identified a gene

of major effect have had something else in common. Unlike schizophrenia, these illnesses (e.g., Duchenne muscular dystrophy and cystic fibrosis) have fairly straightforward diagnostic criteria; that is, their clinical phenotype is well-established. That of schizophrenia is not [9, 50, 79, 87].

The ability to advance our knowledge about schizophrenia has been partially handicapped by our inability to define it precisely and consistently. There is no question that schizophrenia is a 'real disorder' that produces severe and often persistent disabilities. For a variety of historical and conceptual reasons,¹² however, there has been disagreement among clinicians and investigators as to the best ways to define this disorder [9].

In short, the "student of schizophrenia pursues a moving target" [87], and an eminently mobile one at that.

Beginning in 1982, the United States National Institute of Mental Health's journal, *Schizophrenia Bulletin*, ran a series of unsolicited articles by leading schizophrenia researchers under the title "What is Schizophrenia?" As one might imagine, the opinions of the researchers varied greatly. Yet many of them expressed optimism regarding the future of psychiatry. Meltzer [89] was especially hopeful:

In the year 2000, an essay such as this might be able to discuss when in the developmental cycle specific genes and their products, in response to specific exogenous insults or stresses, produced various biochemical and electrophysiological abnormalities that, in turn, were the basis for specific abnormal behaviors in the numerous subtypes of schizophrenia. What a joy it will be to read, what an even greater joy to write, such an essay.

These millenarian hopes have not come to fruition; allow me to suggest a reason why they have not been realized.

In 1974, the American Psychiatric Association (APA) appointed Robert Spitzer as head of its Task Force on Nomenclature [90]. The mandate of the Task Force was to develop and issue the third edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. Wanting (with some justice) a clean break from *DSM-II*, Spitzer demanded of the APA Board of Trustees a Task Force whose membership comprised no one who had helped to create the earlier manual [91]. He chose as Task Force members psychiatrists and psychologists "committed to diagnostic research and not to clinical practice," intellectually rooted in St. Louis and not Vienna [92] – more interested in biological substrates than in clinical phenotypes, or "phenomenotypes" [93].

This focal shift in schizophrenia research helped to facilitate the conceptual and practical slide from the apparent heredity of schizophrenia (based on the indirect and circumstantial evidence of the family, twin, and adoption studies) to genes-plus aetiological models. That is, thanks in part to these changes in psychiatric orientation, the merest suggestion

that schizophrenia is inherited led to the judgment that genes, when environmentally triggered, cause schizophrenia. Then, given this latter conviction, research attention was diverted from the clinical phenomenology of schizophrenia and directed toward its biological substrates, including its putative genetic basis, according to which the aetiology of the disorder is almost universally construed in terms of a diathesis-stressor model.

The imperative to investigate the biological substrates of, and therefore the genetic aetiology of disorders, is deeply embedded in contemporary psychiatry; as Louis Sass [94] has observed, the “tendency to neglect careful description and analysis of abnormal psychological phenomena in favour of a too-quick and too-exclusive focus on etiology or causation” is “a great weakness of twentieth-century psychiatry and psychology.”¹³ And this is so despite the claimed aetiologically atheoretical approach of the *DSM-III-R* and *DSM-IV* [80]. The current repudiation of phenomenology (that is, the current lack of attention to description and analysis at or near the level of the observed behavioral phenomena) is the lasting legacy of the biological, and more recently genetic, revolution in psychiatric research and, I contend, helps to explain our failure to understand schizophrenia. The classical motivation for the aetiological imperative is anaemic at best, and “none of the evidence for a biological mechanism responsible for schizophrenia or any of its symptoms is conclusive. Interest in genes involved in various neurodevelopmental process is based on incomplete evidence and circumstantial inferences” [38]. It may be time, then, to dislodge the aetiological imperative, especially in its genetic incarnation.

Given the failure to establish the putative genetic mechanisms responsible for schizophrenia, the molecular strategy has reached a watershed: either we endorse an untenable and impracticable genetic reductionism and continue to search (apparently in vain) for genetic influences, or we resolve to improve the phenotype of schizophrenia as a necessary condition for any future genetic (or environmental) studies. Cardno and McGuffin [10] would appear to support the former alternative. They contend that while the boundaries of the concept of schizophrenia are unclear, the homogeneity of the illness is debated, and the mode of inheritance remains unknown, we ought nonetheless to conclude that the techniques of molecular genetics, especially those based on recombinant DNA technology, are our best hope for future success in schizophrenia research. Farmer and Owen reach a similar conclusion [73] about the prospects of the HGP.

For the reasons elucidated in this article, I cannot share their optimism, nor can I encourage their persistence. Rather, I concur with the conclusion reached by Tim Crow and Lynn DeLisi after summarizing the results of

both the 1997 and 1998 Chromosome Workshops at the Vth and VIth International Congresses of Psychiatric Genetics:

Perhaps one should conclude from current [unsuccessful] attempts to map genes for schizophrenia and bipolar disorder that it is time to return to hypotheses that relate to the nature of psychosis and what is known or may be hypothesized about its pathology [84].

At present, the linkage strategy is not yielding the strong and consistent leads that had been hoped for 5 to 10 years ago. Other approaches, e.g., through pathophysiological mechanisms, may have to be pursued. Without a hypothesis there may be no way ahead [85].

Others, including Andreasen [9, 86], Kringlen [15], and Lander, acknowledge this fundamental point that “good genetics requires good phenotypes” [95]: for any substantial progress to be made in understanding the aetiology of schizophrenia, “knowing how to describe, define, and recognize it is a necessity” [9]. That is, for molecular genetics to contribute to psychiatry in any important way, we must refine the phenotype of schizophrenia such that we might be better equipped to investigate the possible existence of molecular aetiological mechanisms – assuming that we have good evidence for supposing their existence, and assuming that we have a sufficiently rich model of ontogenesis, that is, one not always or entirely reducible to differential gene expression.¹⁴

In an effort to describe clinical and biological reality as accurately as possible, and to understand both the behavioral phenotype and its psychopathology and aetiology as fully as possible, I thus encourage the return to phenomenology construed as a dialectical interplay [9] between (a) the study of the clinical presentation of schizophrenia (that is, of the actual schizophrenic organism in all his complexity, and not merely his blood, sweat, and DNA),¹⁵ (b) scientific but nonmolecular aspects of nosology (such as biometric and neurological approaches), and – eventually – (c) the use of strategies of molecular genetics and ‘human social ecology’ (as it were), if and where appropriate.

Allow me to conclude by presenting some recent research on the phenotype of schizophrenia which approximates the perspective I envision as most promising in psychiatry. I have noted that the clinical heterogeneity of schizophrenia is very widely accepted. Two schizophrenics can each present with a number of the *DSM-IV* symptoms of schizophrenia, and yet in fact share none of these symptoms with one another. One consequence is that there is some debate, both historical and contemporary, as to whether schizophrenia should be understood as a single disease entity, or in terms of dimensions, or rather in terms of categorical subtypes [86, 96–97]. Moreover, schizophrenia has no objective marker comparable to plaques in Alzheimer’s disease [86]. The clinical diversity and diagnostic ambiguity

of schizophrenia have confounded research at two levels of investigation, the micro-level of genetic mechanisms and the macro-level of observed symptoms. Research into biological substrates of certain symptoms has tended “to focus on one aspect of the disorder while ignoring others (e.g., accounting for hallucinations by invoking the temporal lobe but failing to explain why delusions or various negative symptoms are also present)” [86]. Meanwhile, the search for schizophrenic genes has been hampered by the lack of a discrete phenotype. The recent work of Andreasen and her colleagues [86] is designed to redress these concerns.

Andreasen et al. [86] direct their energy at an intermediate level, proposing that neither the symptoms nor their alleged genetic determinants are primary. Instead, they argue, the phenotype of schizophrenia is best understood as a neurodevelopmental cognitive abnormality – namely, cognitive dysmetria, a timing aberration in a fundamental, highly contextual, extremely sensitive feedback loop; this defect in timing affects a basic neurodevelopmental process upon which memory, attention, and language, for instance, are based, with the result of producing the severe heterogeneous symptoms characteristic of schizophrenia.

Thus do Andreasen et al. [86] propose an understanding of schizophrenia very much immune to the criticisms raised in this article of too much schizophrenia research. First, it is noteworthy that this research does not draw its motivation from flawed family, twin, and adoption studies; though cognitive dysmetria may very well turn out to be inherited, this is not predecided by prior commitment to a hypothesis about its transmission – and therefore we are not saddled with the impetus to find schizophrenia genes. Secondly, though Andreasen et al. do not focus on the genetic level, this is not to suggest that the genetics of cognitive development are unimportant or irrelevant, for deeply entrenched mechanisms involved in the development of fundamental cognitive activity in humans are surely code-termined by the activities of genes-in-developmental-context. But note that this admission has no bearing on the appropriate methodology for investigating such mechanisms; cognitive dysmetria does not require, *a priori*, a lower-level explanation based on genes. As Andreasen et al. evince, these mechanisms are worth investigating on their own terms, for the reinterpretation of the symptoms of schizophrenia as sharing an underlying endophenotypic – though perhaps not genotypic – substrate is an important advance in schizophrenia research.

Hence the final advantage of Andreasen et al.’s proposal: this meso-level phenotype – identified on the basis of the complex interplay of clinical observation, theoretical neurobiology and neuropathology, and neuroimaging techniques such as positron emission topography and mag-

netic resonance imaging – will surely generate additional research into the intricate neurodevelopmental processes involved in the aetiology of schizophrenia. At the very least, the cognitive dysmetria phenotype can be elucidated in detail so as to facilitate new studies in both human social ecology and in molecular genetics, though we must keep in mind the challenge of developmental systems theory to any simplistic model of gene action. In sum, the Human Genome Project and the techniques of molecular genetics may well eventually contribute to our overall understanding of schizophrenia, but only in the context of a sufficiently well-elaborated phenotype, a genuine openness to the possibility of specific nongenetic determinants of schizophrenia, and an appropriately robust psychiatry concerned, first and foremost, with environmentally embedded organisms and not merely their DNA.

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NOTES

¹ For economy's sake, I will refer to the family, twin, and adoption studies of schizophrenia as 'classical studies,' though some authors prefer the phrase 'epidemiological studies.' What may more properly be called 'epidemiological studies' of schizophrenia – namely, population studies of incidence such as the World Health Organization ten-country study [6] – are beyond the scope of this article.

² This is, of course, not surprising, given the role of genes in the development of almost all human traits from the simplest to the most complex! Difficulties arise only in trying to tease apart the relative contributions of genes and environments construed as independent determinants of traits. See discussion below.

³ See Kendler and Gardner [11] for a recent defense of twin studies in schizophrenia research, particularly of the equal environment assumption (that MZ twins experience an [external] environment no more similar than that experienced by DZ twins); though Kendler and Gardner dismiss criticisms of this approach, their discussion is remarkable in

that they caution researchers not merely to assume the validity of the equal environment assumption, but rather to evaluate its merits and demerits. Nevertheless, the equal environment assumption is insensitive to the differences between MZ and DZ twins in their internal (*in utero*, e.g.) environments which may well contribute to the excess resemblance of MZ twins as compared to DZ twins.

⁴ In the case of pairwise concordance, concordant twins are counted as one pair in the numerator and one pair in the denominator. In the case of probandwise concordance, twins who are both schizophrenic – as long as they were individually located (e.g., independently identified from a register of schizophrenics) – are counted as two pairs in the numerator and two pairs in the denominator [12]. Boyle notes that these two methods of measuring concordance ask different questions of the data: the pairwise method asks “in what proportion of pairs are both called schizophrenic?” while the probandwise method asks “in what proportion of pairs is there a ‘schizophrenic’ co-twin?” [5; Boyle uses the scare-quotes to signify what is for her the questionable status of the concept of schizophrenia]. If A and B are schizophrenic twins and are both found during the initial search for probands, they will be counted as one pair according to the pairwise method (A and B are concordant), and two pairs according to the probandwise method (A is concordant with B and B is concordant with A). There is a debate over which method is preferable. According to Gottesman, the probandwise method is technically more correct, and also more genetically informative [12] – though he offers no argument for this claim. For a discussion of this dispute, see [5]. For a criticism of the method Gottesman champions, see [4] and [13].

⁵ The evidence for viewing schizophrenia as caused by an infection is equivocal. Some [e.g., 27] have held that schizophrenia is caused (in some cases at least) by a maternal viral infection, and they offer the 1957 influenza epidemic as evidence for their claim; Crow [28] is critical of these studies. Davis and Phelps [26] do not specify a particular kind of infection. Ewald [29] has long since promoted infection as the cause of schizophrenia and other illnesses. Recently, Suvisaari et al. [30] have shown an association between the incidence of paralytic poliomyelitis and the subsequent incidence of births (five months later) of individuals who eventually were diagnosed with schizophrenia.

⁶ Gottesman [14] is particularly annoyed by this dimension of the dispute: “in modern times at least, research into the causes of coronary heart disease, non-insulin dependent diabetes and Alzheimer’s disease has not had to contend with the assertion that these diseases are ‘myths,’ or are ‘labels’ used to maintain an unfair social class structure, or result simply from one or another kind of psychic stress traceable to how your mother raised you or how your parents communicated with each other in your presence.” In response to such criticisms as he has noted, Gottesman is reduced to hurling epithets, claiming that the trouble is with “marxist philosophers, orthodox psychoanalysts, and assorted ideologues” who “would rather grind their own axes than further the impartial quest for the causes of schizophrenia”. Which is, of course, to beg the question.

⁷ As Gottesman remarks [12], “largely as a consequence of the Dorado Beach conference [Puerto Rico, 1967], the entire field of schizophreniology was converted, at least in public pronouncements, to some kind of interactionist stance for advancing against the common enemy – ignorance about the true causes of schizophrenia.”

⁸ I am grateful to Lisa Gannett for encouraging me to try to be clearer about the various senses of ‘interactionism’ which are occasionally conflated in the literature. She also graciously supplied a very helpful unpublished manuscript.

⁹ See Sarkar [44], chapter 4, for a trenchant critique of quantitative genetic efforts to separate genetic and environmental influences.

¹⁰ Gottesman himself holds that the identification of “genes that contribute to the etiology

of behavioral disorders ... will inevitably follow from the results of the Human Genome Project" [64].

¹¹ By the same token, a predisposition is neither in the genes nor in the environment, but rather in their fortuitous (or, rather, disastrous) interaction.

¹² For discussion, see, e.g., [5, 88].

¹³ To be sure, the central focus on aetiology was a problem with the pre-genetic era in psychiatry, as well; proponents of psychoanalytic approaches were preoccupied with establishing a causal and explanatory framework for interpreting mental illness [80].

¹⁴ There is a further question about the degree to which our nosologic categories will (or ought to) change in light of genetic research; for some thoughtful remarks (with which I occasionally disagree, for reasons which may be evident from the foregoing), consult Harris and Schaffner [80].

¹⁵ Young [90] makes a similar observation regarding the biological investigation of post-traumatic stress disorder: "To obtain facts and findings, researchers now interrogate blood and urine rather than men."

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