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GENETIC MODELS OF MENTAL ILLNESS

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Introduction

When the long-standing "nature versus nurture" controversy in psychiatry was finally resolved by the adoption studies, demonstrating beyond a reasonable doubt the genetic predisposition to the major mental disorders, attention finally turned to the more productive question of how both genetic and environmental factors are involved in transmitting disease; that is, transmission models.

The earliest of these transmission models were Mendel's laws of inheritance, and early workers in psychiatric genetics naturally attempted to apply these models to the diseases they were studying. However, unlike many medical diseases that fit the Mendelian ratios with such precision that another explanation would be hard to imagine, none of the psychiatric disorders gave an acceptable fit. This led to models modifying Mendel's laws by postulating such variables as incomplete penetrance and additional genes. These explanations were never widely accepted, probably because enough modifications could make the model fit almost any data set and, moreover, no means existed for statistically testing the fit with a probability level.

A major development occurred in the 1960s with the adaptation of the laws of quantitative genetics to the study of discrete traits; that is, the multifactorial threshold model. In the 1970s, this model was expanded to incorporate multiple disease forms, sex differences, and most important, it was rendered statistically testable for goodness of fit. Meanwhile, sophisticated single-locus models that lent themselves to statistical testing were also developed. Finally, the increasing availability of computers made possible analyses that would have been impossible in the early days of model construction.

The term “transmission model” is preferred to “genetic model” because the models do not necessarily require an assumption that the disorder is genetic. Analysis by transmission models is entirely appropriate for conditions of undetermined etiology, even when they may be purely environmental. A transmission model is basically a mathematical hypothesis —a set of predictions based on an assumption about the transmission of the disorder that can be compared with observed data and the fit of model to data tested with a statistic so that the model can be accepted or rejected.

A model is defined by a set of parameters such as the frequency of the trait in the population. The parameters and the assumptions of the model comprise a mathematical formula, or set of formulas that, for any set of parameter values, generate expected values of affected persons among

various classes of relatives and the population. Data collected on disease prevalence in the population and in these classes of relatives of affected persons provide the observed values against which the model is tested. The parameters are iterated over a series of values, successive values being substituted for each parameter until the set of parameters giving the best fit of expected to observed values is obtained. The fit can be maximized in either of two ways. First, differences between observed and expected values may be used to compute a chi-square for each parameter set; the parameter set yielding the smallest chi-square is the best fitting one. Alternatively, a likelihood approach may be employed. Under the model, and for each parameter set, the probability of the observed numbers of affected and unaffected persons in each pedigree can be calculated. The product of these probabilities across pedigrees is referred to as the likelihood and is maximized by the best fitting parameter set. Finally, the goodness of fit of the best fitting parameter set is tested statistically to determine whether the model is accepted or rejected. In order to test fit, the degrees of freedom must be determined. They are equal to the number of classes of independent observations minus the number of parameters defining the model. If the number of observations exactly equals the number of parameters, there are o degrees of freedom and the model cannot be tested. In the chi-square analysis, the probability level of the smallest chi-square value with its respective degrees of freedom determines whether the model provides an acceptable fit.

In the likelihood approach, a likelihood ratio is constructed by the likelihood of the parameter set tested divided by the likelihood of an "unrestricted model" that provides a perfect fit to the data. Twice the logarithm of the likelihood ratio is asymptotically distributed as a chi-square with its respective degrees of freedom.

Slater and Cowie proposed a single gene model of schizophrenia that in some respects represented a forerunner of present transmission models and exemplifies many of these principles. The model proposes a single gene *a* of frequency *p* and its normal allele *A* of frequency 1 — *p.* Thus, three genotypes are possible: *AA, Aa,* and *aa,* which the law of Hardy-Weinberg equilibrium predicts will occur in the following frequencies respectively: $(1 — p)^2$, $2p(i — p)$, and p^2, the three frequencies summing to unity. If *m* is the proportion of heterozygotes *(Aa)* who develop schizophrenia, then the prevalence of schizophrenia in the population can be expressed by the following formula: $s = 2mp(1 — p) + p^2$. With *s* fixed at 0.0085, population prevalence of schizophrenia, *m* can be calculated from any given value of *p.* In this way, a wide range of parameter sets of *p* and *m* were used to calculate the expected rate of schizophrenia for various classes of relatives of schizophrenics: children, siblings, and second- and third-degree relatives. The expected and observed values were compared by visual inspection rather than a statistical test, and it was concluded that when $p — 0.03$ and $m = 0.13$, a suitable fit was obtained.

Use of Transmission Models

Transmission models have been applied to a number of questions in psychiatry, the problems addressed falling into the following categories.

1. Do the data favor single gene or multifactorial transmission? None of the psychiatric disorders fit classic Mendelian segregation ratios, and family studies have been compatible with either a partially penetrant gene or with multifactorial inheritance. With transmission models, the fit between model and data can be expressed quantitatively as a probability level, and in this way different models can be compared and poorly fitting ones rejected.

2. Are the data compatible with a specific genetic or environmental hypothesis? Although the only method for definitively separating heredity from environment is the adoption study, specific hypotheses about genetic and environmental influences can be formulated and tested. For instance, are women less likely to develop antisocial personality or alcoholism because social pressures against this behavior are greater in women or because they are inherently more resistant to the disorder? Each hypothesis predicts different patterns of transmission that may be used to determine which best fits the data.

3. Can two or more conditions be considered sub-forms of a single disorder? Disorders in psychiatry that may be conceptualized in this way include unipolar and bipolar affective disorder within bipolar families, antisocial

personality and hysteria, and male and female alcoholism. Disorders such as these that differ with respect to severity, frequency, or symptomatology but occur together in families can be analyzed to determine whether a single transmission model can account for both or whether separate disorders segregating independently must be assumed.

4. Can mild and atypical forms of a disorder be included as a "spectrum" of that disorder? Examples of such conditions include schizoid traits in relatives of schizophrenics, as well as cyclothymic personality and mild, atypical depressions in relatives of manic-depressives. If these conditions are transmitted independently of the major disorder, the transmission hypothesis may be rejected.

In interpreting the results of studies using transmission models, several points must be kept in mind. First, when a model provides an acceptable fit to the data, this does not mean that it is the only explanation for the observations. Other models not tested, or not yet constructed, may account for the data equally well. Moreover, the disease may subsequently prove to be heterogeneous, with each subtype being transmitted in a manner different from what had originally been thought. Second, if a model does not fit the data, it must be remembered that what has been rejected is that particular model. Thus, rejection of a specific model of environmental transmission does not mean that environmental transmission has been disproven, but only that the formulation of environmental transmission by that model does not

account for the data. Finally, data sets in psychiatry often vary greatly from one investigation to another, and models fitting one data set may not fit another of the same disease.

Overview of Transmission Models

This section will present an overview of the transmission models commonly encountered in the psychiatric literature. The following section will review the literature on the actual application of these models. The presentation will be limited to models that have been applied to psychiatric data; models that have been presented in theory only are omitted. The relevant models can be conveniently divided into single-locus and multifactorial ones.

Multifactorial Models

One Threshold

The multifactorial threshold model was originally proposed by Carter in 1961, developed into a quantitative mathematical model by Falconer in 1965, and extended to include multiple thresholds by Reich and associates in 1972. This latter development rendered the model testable against data and it has been widely applied in psychiatry since that time. Since the models currently in use in psychiatry were developed by Reich, his notation will be followed.

Basically, the model postulates that multiple genes plus environmental factors contribute to a continuous liability which, although not measurable, is normally distributed in the population, with individuals exceeding a hypothetical threshold manifesting the trait, and those falling short of the threshold liability being unaffected. This formulation is presented diagrammatically in figure 4-1, with the area to the right of the threshold (*T)* representing the affected portion of the population.

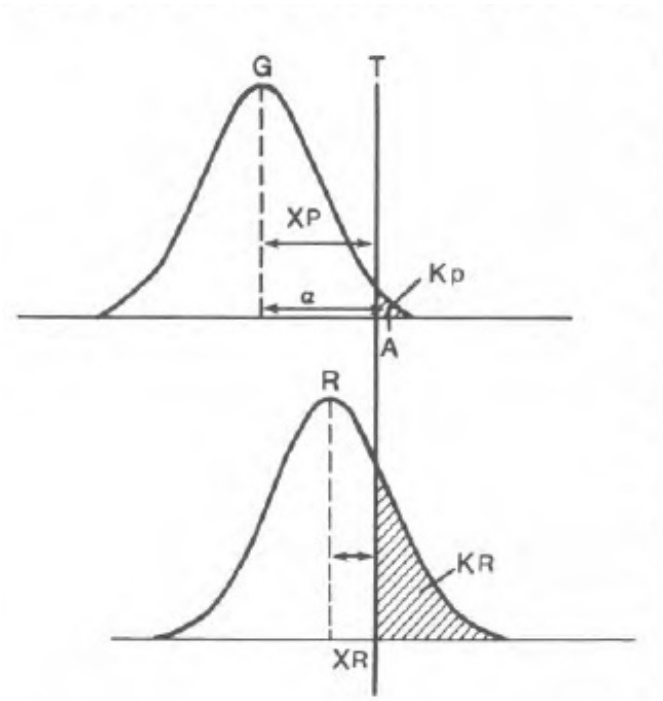

FIGURE 4-1.
The Multifactorial Single Threshold Model. The upper distribution

represents the liability of the general population and the lower distribution that of the relatives of affected individuals. G and R are the liability distribution means of the general population and of the relatives of affected individuals, respectively. T is the threshold. Kr* and KH are the prevalences of the trait in the population and among relatives of affected individuals, respectively. XP and are the deviations of the threshold from the population and relative means respectively. A is the mean liability of affected individuals in the population, and a is its deviation from the general population mean.

*This chapter retains Reich's original notation using an upper case P to designate population parameters. However, in more recent publications a lower case p is used. The two refer to the same parameter ($K_P = K_P$).

SOURCE: Reich, T., Cloninger, C.R., and Guze, S.P. "The Multifactorial Model of Disease Transmission: I. Description of the Model and Its Use in Psychiatry," British Journal of Psychiatry, 127 (1975): 2.

Reich and associates have summarized the assumptions on which the model is based: (1) the relevant genetic and environmental factors can be combined into a single continuous liability variable; (2) the liability is normally distributed; (3) a threshold in the liability divides the population into affected and unaffected classes; (4) the relevant genes are each of small effect and act additively; (5) environmental factors are also of small effect and act additively; and (6) since environmental factors may be shared by relatives, the disease may be partly to entirely nongenetic.

In figure 4-1, the upper curve represents the liability distribution of the population, and the lower one, that of first-degree relatives of affected persons. The lower curve is displaced to the right, resulting in a higher prevalence of the trait in the first-degree relatives of affected persons than in

the population; that is, the trait is familial. The more strongly familial the disorder is, the farther to the right the relatives' distribution is displaced. This relationship can be expressed as a phenotypic correlation (r). Where K_P and K_R represent the prevalence of the trait in the population and in first-degree relatives of affected persons, respectively, Xp and Xr, the deviation of their respective population means *(G* and *R)* from the threshold *(T),* and *a* is the mean deviation of the probands from the population mean:

$$r = \frac{X_P - X_R}{\sqrt{1 - (X_P^2 - X_R^2)\,(1 - X_P/a)}\,/\,(a + X_R^2(a - X_P))} \qquad [4\text{–}1]$$

The values of X_R, X_P, and a can be obtained from tables once the population prevalences (K_P and K_R) are known. The correlation, which can be readily derived from these values, varies from 0 to 1, with 1 indicating that all relatives are affected and o indicating that relatives experience the same prevalence as the population.

The model can be fit to data by calculating the heritability (h^2) for correlations between various classes of relatives. This parameter is based on the assumption that the total variance in a trait can be partitioned into genetic and environmental variance ($V_T = V_G + V_E$). The heritability represents the proportion of total variance due to additive genetic variance[1] ($h^2 — V_A/V_T$). It

can be estimated by dividing the correlation between relatives by the coefficient of genetic relationship (1 for monozygote twins, 1/2 for first-degree relatives, 1/4 for second-degree relatives, and so forth). The model predicts that the heritabilities should be consistent across various classes of relatives (for the same trait in the same environment). If this proves to be the case, then the model can be said to fit the data.

The major contribution of this model has been that it greatly modified traditional ways of viewing qualitative traits such as disease. However, it has the disadvantage that with two parameters *(K_P* and *r)* and two sets of independent observations *(K_P* and *K_R),* there are 0 degrees of freedom remaining for statistical testing. Being untestable, the model has been of mainly heuristic value. The problem of non-testability, however, was circumvented by Reich and coworkers, who extended the model to include multiple thresholds.

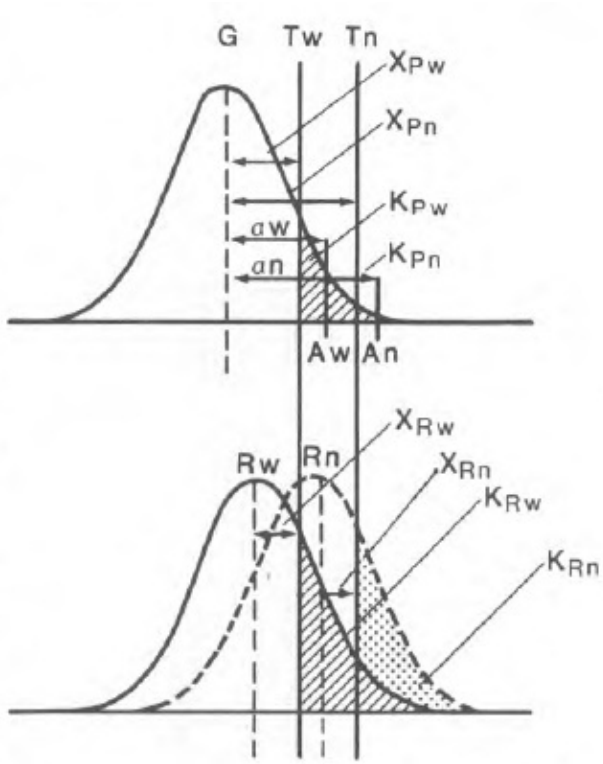

FIGURE 4-2.
The Multifactorial Two Threshold Model. The upper distribution represents the liability of the general population, and the lower two distributions that of the relatives o f individuals with wide and narrow forms of the trait, respectively. The parameters are listed in table 4-1.

SOURCE: Reich, T., Cloninger, C.R., and Guze, S.P. "The Multifactorial Model of Disease Transmission: I. Description of the Model and Its Use in Psychiatry," British Journal o f Psychiatry, 127(1975): 5.

The Multifactorial Multiple Threshold Model

Many traits occur in two forms: a less frequent severe form and a more common mild one. For example, in bipolar families, unipolar depression is approximately twice as common as bipolar illness. This situation can be represented by a continuous liability distribution with two thresholds, which is illustrated in figure 4-2. The parameters are defined in table 4-1. This figure is analogous to figure 4-1, with the upper distribution representing the liability distribution of the population and the lower two distributions that of first-degree relatives of persons with either form of the trait and those with only the severe form, respectively. Persons having either form of the trait are designated as having the wide form *(w)* and are represented by the area to the right of the wide threshold *(T_w).* Those with only the severe subtype are designated narrow form (*n)* and are represented by the area under the curve to the right of the narrow threshold *(T_n).* Those with the mild subtype only are designated wide but not narrow (*w—n)* and are represented by the area between the two thresholds. It can be seen that the liability distribution of relatives of narrow-form probands is displaced to the right of that of the relatives of wide-form probands, resulting in a larger proportion exceeding both thresholds and thus being affected with both forms of the trait. The liability distribution of relatives of wide-form probands is in turn displaced to the right of the population distribution, making their risk for both forms greater than the population but less than relatives of narrow-form probands. The model is completely defined by three parameters: the population

prevalence of the narrow form (K_{Pn}), the population prevalence of the wide form (K_{Pw}), and the correlation coefficient *(r)*.[2] The correlation coefficient can be estimated for subjects with the same form of the illness (that is, between wide-form probands and their relatives with respect to wide-form trait, r_{ww}; and between narrow-form probands and their relatives with respect to narrow-form trait, r_{nn}) with formula 4-1. The cross correlations (between wide-form probands and their relatives with respect to narrow-form trait, r_{wn}; and between narrow-form probands and their relatives with respect to wide-form trait, r_{nw}) can be estimated with the following formulas:

$$r = \frac{X_{Pn} - X'_{Rn}}{\sqrt{1 - (X^2_{Pn} - X'^2_{Rn})\,(1 - X_{Pw}/a_w)}\,/\,(a_w + X'^2_{Rn}\,(a_w - X_{Pw}))} \quad [4\text{–}2]$$

$$r = \frac{X_{Pw} - X'_{Rw}}{\sqrt{1 - (X^2_{Pw} - X'^2_{Rw})\,(1 - X_{Pn}/a_n)}\,/\,(a_n + X'^2_{Rw}\,(a_n - X_{Pn}))} \quad [4\text{–}3]$$

Table 4-1 Parameters of the Multifactorial Two-Threshold Model

G, R_w, R_n	Distribution means for the general population, and for relatives of wide- and narrow-trait probands
T_w, T_n	Wide and narrow thresholds
X_{Pw}, X_{Pn}	Population prevalences of wide and narrow traits
K_{Rw},	Prevalences of wide trait in relatives of wide probands and narrow trait in

K_{Rn}	relatives of narrow probands
K'_{Rw},	Prevalences of wide trait in
K_{Rn}	relatives of narrow probands and narrow trait in relatives of wide probands
X_{Pw}, X_{Pn},	The normal deviate of the
X_{Rw}, X_{Rn},	respective distribution means
X_{Rw},	from the wide and narrow
X_{Rn}	thresholds respectively
A_w, A_n	Mean liability of wide- and narrow-trait individuals in the general population
a_w, a_n	Deviation of mean liabilities, *Aw* and *An,* from general population mean

If the assumptions of the model are correct, and the trait is indeed a unitary one, all four correlations will be equal. Since there are six classes of independent observations (K_{pn}, K_{pw}, K_{Pw} - K_{pn}, K_{Rn}, K_{Rw}, K_{Rw} - K_{Rn}) and three parameters defining the model (K_{Pn}, K_{Pw}, r) there are three degrees of freedom remaining for testing goodness of fit. Thus, the multiple threshold model represents an important advance because it can be statistically tested and rejected if it does not fit the observations. The usual test statistic is the chi-square goodness-of-fit test.

A simple extension incorporates sex effect into the model. The usual situation is a trait such as unipolar depression in which the prevalence differs

between the sexes. This can be represented by a single liability distribution with separate thresholds for the two sexes *(T_m* and *T_f).* With the problem set up in this fashion, the prevalence of the less frequently affected sex represents the narrow form and that of the other, the wide form. This model is defined by three parameters: the population prevalence in males *(K_m),* the population prevalence in females *(K_f),* and the correlation between relatives (*r*). There are six classes of independent observations (the male and female population prevalences and the prevalence among male and female relatives of each sex of proband), leaving three degrees of freedom for testing goodness of fit.

A further extension of the multifactorial model permits the testing of three hypotheses about subtypes of a trait: (1) the subtypes are different degrees of the same process; (2) they are environmental variants of the same process; or (3) they are transmitted independent of one another. These three hypotheses conform respectively to what is termed (1) the isocorrelational model, (2) the environmental model, and (3) the independent model.

The isocorrelational model assumes that familial transmission factors (genetic and environmental) act equally on all subtypes and that extrafamilial environmental factors likewise affect all subtypes equally. If these assumptions are correct, then all four correlation coefficients should be equal: $r_{ww} = r_{nw} = r_{wn} = r_{nn}$. The model is defined by the three parameters K_{pw}, K_{pn}, and *r.*

In the environmental model, extrafamilial environmental factors are assumed to act preferentially on one sub-form of the trait so that: $r_{ww} \neq r_{nn}$. In this model the remaining two correlations are equal and are equivalent to the geometric mean of the first two: $r_{wn} = r_{nw} = \sqrt{r_{ww} r_{nn}}$. The model is defined by the four parameters K_{Pw}, K_{Pn}, r_{ww}, and r_{nn}.

In the independent model, the familial factors (genetic and environmental) responsible for transmission are assumed to differ between the subtypes of the trait. Thus, the subtypes are to a greater or lesser extent transmitted independent of one another and each has its own liability distribution with one threshold. The assumption that the correlation in familial factors between subtypes is less than 1 requires that r_{wn} and r_{nw} be significantly less than $\sqrt{r_{ww} r_{nm}}$ as predicted by the environmental model. Thus, the model is defined by five parameters: K_{pw}, K_{pn}, r_{ww}, r_{nn}, and r_{wn}. If the model is accepted, the degree of overlap between the two trait forms *(w — n* and *n)* can be estimated by the phenotypic correlation which varies from o with complete independence to 1 with complete overlap.

$$r_P = \frac{r_{w-n,\ n}}{\sqrt{r_{w-n,\ w-n}\ r_{nn}}}$$

The three models are nested within each other: the isocorrelational

model represents a special case of the environmental model, which, in turn, is a special case of the independent model. In practice, the isocorrelational model is tested first since it is the most restrictive. If it is rejected the environmental model is tested and, in turn, if it can be rejected, the independent model is tested.

Single-Locus Models

The earliest single-locus model bearing any resemblance to present-day transmission models is the formulation by Slater, which was presented earlier. Since both Slater's single-locus model and Falconer's multifactorial threshold model appeared to fit the data, Slater developed a computational model for determining whether a data set favored single-gene or multifactorial inheritance. Although itself not a transmission model, this method has been widely used in psychiatry to analyze transmission and, therefore, will be included in this review.

Slater reasoned that if a trait is transmitted as a single gene, then ancestral secondary cases should appear predominantly on one side of the pedigree (paternal or maternal). In polygenic inheritance, secondary cases should appear on both sides more frequently than in single-gene transmission. A rigorous solution was not possible, but by using some simplifying assumptions he arrived at the expectation that in polygenic

inheritance pairs of ancestral cases should be unilaterally distributed approximately twice as frequently as bilaterally. Any deviation from this expected two to one ratio in the direction of excess unilateral pairs would be evidence for single-gene transmission, and the deviation could be statistically tested with a chi-square test. Slater and Tsuang subsequently introduced a correction factor to allow for the greater weight given to families with large numbers of secondary cases.

As the multifactorial model developed in sophistication, more advanced single-locus models were being developed. Cavalli-Sforza and Kidd developed a single-locus threshold model resembling in some respects the multifactorial threshold model. The model, illustrated in figure 4-3, proposes a single locus with two alleles *A* and *a,* producing the three genotypes *AA, Aa,* and *aa* with frequencies determined by Hardy-Weinberg equilibrium: $(1 — q)^2$, *2q(i — q),* and q^2, respectively where *q* is the gene frequency of the *a* allele. Each genotype mean is represented on a liability scale, with the *AA* mean arbitrarily set at 0 and the *aa* mean at *2;* the *Aa* mean occupies a variable distance between the two, its distance from 0 being represented by *h',* which can vary from o for complete recessiveness *(Aa = AA)* to *2* for complete dominance *(Aa = aa).* Environmental variance causes the phenotypic liability values of each genotype to vary, forming a distribution of values around each genotype mean. The three distributions are assumed to each be normal with equal variances represented by ϵ^2. The three overlapping liability distributions form

a continuous distribution of liability that is divided by a threshold *T* into affected and unaffected classes. Thus, the model is defined by four parameters: gene frequency *(q),* dominance *(h'),* environmental variance *(ϵ^2),* and threshold position *(T).*

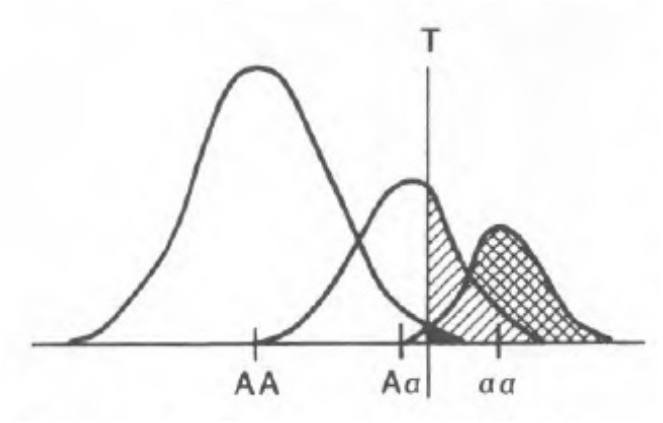

Figure 4-3.
The Single-Locus Threshold Model. The three distributions represent the liability of AA, Aa, and aa individuals, respectively. The position of AA is arbitrarily set at o and that of aa at 2. The parameters defining the model are: gene frequency of a allele (q); environmental variance (e2); position of the heterozygote Aa (h); and threshold position (T).

Source: Kidd, K.K., and Cavalli-Sforza, L.L. "An Analysis of the Genetics of Schizophrenia," Social Biology, 20(1973): 256.

Expected numbers of affected relatives in various classes can be calculated for any set of parameter values. The model determines the probability of an affected, or unaffected, person being of each genotype. For each genotype, the probability of any class of relative sharing either allele

with the proband can be calculated. Finally, for each possible genotype of a relative, the model determines the probability of being affected. A computer program is used to iterate over the parameters, generate the expected values for each parameter set, compare them with the observed ones, and calculate the chi-square for goodness of fit.

Elston and associates developed models for a limited number of loci (two autosomal and one sex-linked) based on segregation analysis using a likelihood approach. The single locus model proposes two alleles *A* and *a* resulting in the three genotypes *AA, Aa,* and *aa* in Hardy-Weinberg equilibrium with *q* the frequency of the *A* allele. The probability of being susceptible is represented by λ, which can be made to vary with genotype or to be independent of genotype. Age of onset is considered to be lognormally distributed (the logarithm of the age of onset is normally distributed) with mean μ which may either vary with genotype or be independent of genotype. All age of onset distributions have the same standard deviation σ. The probability of transmitting the *A* allele is represented by *T*, which, for the three genotypes, assuming Mendelian inheritance, is $T_{AA,A} = 1$, $T_{Aa,A} = 1/2$, and $T_{aa,A} = 0$. Likewise, there are three complementary probabilities of transmitting the *a* allele. Finally, an ascertainment parameter *K* is introduced to correct for ascertainment bias.

The model accepts either dichotomous (affected, unaffected) or

trichotomous (affected state 1, affected state *2,* unaffected) traits. Two hypotheses are tested. The Mendelian hypothesis assumes transmission probabilities *(*$T_{AA,A}$ = 1; $T_{Aa,A}$ = ½; and $T_{aa,A}$ = 0) in accordance with Mendel's law. The environmental hypothesis assumes that the probability of transmitting the trait is independent of genotype and, therefore, that the three transmission probabilities are equal *(*$T_{AA,A} = T_{Aa,A} = T_{aa,A}$*).* A computer program calculates the likelihood of the data set under each hypothesis and under an unrestricted model, which allows the parameters to vary independently of one another to provide a perfect fit to the data. The Mendelian and environmental hypotheses are tested by means of a likelihood ratio with the unrestricted model. A small likelihood ratio implies a small departure from the unrestricted model and, thus, a good fit to the data and can be tested by the chi-square (2 log [likelihood ratio]).

It can be seen from this brief overview that as transmission models have become more advanced, they have expanded the range of testable hypotheses about disease transmission by incorporating such variables as multiple forms of a trait, environmental effects, and age of onset. Consequently, each transmission model subsumes a number of hypotheses within it. In this sense most of the early hypotheses of single gene (or polygenic) inheritance are tested when one of these broader transmission models is applied. Finally, the single-locus and the multifactorial models represent the extremes of a continuum of potential models from one gene to many. However, until the

extremes can be rejected, there is little value in constructing new models with two loci, multiple alleles, and so forth, which, although heuristically less valuable, will fit the data equally well.

Table 4-2 Parameters of the Elston Segregation Analysis Model

$T_{AA,A;}$	Probability of each
$T_{Aa,A;}$	respective genotype
$T_{aa,A}$	transmitting the *A* allele to progeny
q	Gene frequency of the *A* allele
y	Probability that an individual will develop the trait if he or she lives long enough
μAA, μAa, μaa	Mean age of onset of each
	respective genotype on a log scale
σ	Standard deviation of the logarithm of age of onset
K	Ascertainment parameter

Application of Transmission Models

This section will review the application of transmission models to data on schizophrenia, affective disorder, antisocial personality, hysteria, alcoholism, and panic disorder. These studies illustrate the models presented in theory in the last section, as well as their application to the field of psychiatry. The review should also familiarize the reader with recent research

in this area. Space does not permit a detailed analysis of each study. However, examples of the major models are reviewed in sufficient detail to provide an understanding in some depth of the use of the models. (For those interested in pursuing the original literature, all of the major studies are reviewed and referenced.)

Schizophrenia

Schizophrenia was a major interest to the early workers in psychiatric genetics who attempted to adapt Mendel's laws to their data. Kallman proposed that an autosomal recessive gene accounted for the inheritance of schizophrenia in his study of a large collection of kindreds. Böök proposed that a single gene with incomplete penetrance accounted for the inheritance of schizophrenia and demonstrated that the model fit his data when the heterozygote penetrance was 0.2, the homozygote penetrance 1, and the gene frequency 0.07. However, because of the unusually high population prevalence in Böök's material, his model would not have fit the data of other workers.

Slater further developed the model of a single partially penetrant gene into his formulation (see "Introduction"). He fit the model to data derived from the literature dealing with children of one and two schizophrenic parents, siblings of schizophrenics, and second- and third-degree relatives.

Taking 0.0085 the population prevalence of schizophrenia (5), various values for the gene frequency (*p)* were substituted into the formula $S = 2mp(1 — p) + p^2$ and values of the heterozygote penetrance *(m)* calculated. When these parameter sets were used to calculate the expected rates of schizophrenia in the aforementioned classes of relatives, the model seemed to give a good fit at a gene frequency of 0.03 and a penetrance of 0.13. Thus, the model predicted a relatively uncommon gene that was predominantly recessive.

Slater felt that his model accounted for the data as well as the polygenic threshold model and tested the two with his computational model. Nineteen schizophrenic kindreds from the Maudsley Hospital were analyzed, and a unilateral to bilateral ratio of 42 to 11 was found, which was significantly greater than the 2 to 1 ratio predicted by polygenic inheritance. Thus data favored the single locus model. Since the first study was based on family history, Tsuang applied the model to data obtained from interviews. The twenty-three kindreds in his study revealed a ratio of 43 to 11 unilateral to bilateral pairs, again significantly favoring single-gene transmission.

Gottesman applied Falconer's multifactorial single threshold model to the inheritance of schizophrenia. Data were taken from the literature on monozygotic and dizygotic twins, first-degree and second-degree relatives. Calculations were carried out using a population prevalence of schizophrenia (*q)* of both 1 percent and 2 percent. Since the model is defined by q and h^2,

with q fixed, h^2 can be calculated from the correlation in prevalence between probands and any class of relatives. If the model is to fit, the heritabilities should be consistent across classes of relatives and this was found. At a 1 percent prevalence, h^2 estimates on age-corrected data ranged from 79 percent among first-degree relatives to 106 percent for one set of twins. The consistency was acceptable, especially considering that the data came from five investigations in three countries. The heritabilities indicated a substantial genetic predisposition to schizophrenia. They have been subsequently recalculated on twin data using the tetrachoric correlation, which is more exact than the Falconer method used by Gottesman. Again, both a 1 and 2 percent population prevalence was used in the calculations. At a 1 percent prevalence, the heritabilities ranged from 80 percent to 93 percent, substantiating Gottesman's analysis.

Heston proposed a single-gene model that assumed complete penetrance of the gene. The model made use of the observation that the nonschizophrenic relatives of schizophrenics often manifest other forms of psychopathology, which he termed "schizoidia." If the sum prevalence of schizophrenia and schizoidia was taken, in those studies that recorded this data, the observed proportions of affected relatives came surprisingly close to that predicted by simple autosomal dominance. For children, 49 percent were affected, compared with 50 percent expected, and the respective figures for siblings were 46 percent versus 50 percent; for parents, 44 percent versus 50

percent; for children of two schizophrenic parents, 66 percent versus 75 percent; and for monozygotic co-twins of schizophrenics, 88 percent versus 100 percent.

Using pooled data from the literature on children, siblings, second-degree relatives, and mono- and di-zygotic co-twins of schizophrenics, Kidd and Cavalli-Sforza and Matthysse and Kidd applied the single locus threshold model to schizophrenia. They noted considerable heterogeneity in prevalence rates among investigations and dealt with the problem by fitting the model to both a set of "low" and "high" rates. The four parameters of the model, gene frequency *(q),* environmental variance (ϵ^2), dominance *(h'),* and threshold position (J), led to a number of parameter sets all fitting the data. For illustrative purposes one of these parameter sets will be discussed in detail: q = 0.10, ϵ^2 = 0.36, h' = 0.25, and T = 1.6. It will be remembered that the *AA* mean is arbitrarily set at 0 on the liability scale and the *aa* mean at 2.0, with *Aa* falling somewhere in between, its position determined by h' (0.25). This arbitrary scale can be standardized by using the standard deviation (S.D.) as the unit of measure, which in this case is 0.6 ($\sqrt{0.36}$). The threshold *(T* = 1.6) lies 2.7 S.D. above the *AA* mean and 2.25 S.D. above the *Aa* mean. Thus, relatively few *AA* and *Aa* genotypes will exceed the threshold, and most persons with the disease will be *aa,* the mean of their liability distribution lying 67 S.D. above the threshold. Finally, the gene is a common one, with frequency 0.10, meaning 19 percent of the population will carry it [q^2 + 2q(1

— q)].

Returning to the overall analysis, all parameter sets predicted a relatively common predominantly recessive gene, as in the illustration. Although persons of the normal *AA* genotype had a small likelihood of developing schizophrenia, 16 to 25 percent of schizophrenics were *AA* depending on the parameter set. (Although proportionally less *AA* are affected, they constitute the majority of the population and, thus, contribute a substantial number of cases.) Thus, the model predicted a sizable proportion of sporadic cases. Another interesting finding was that the expected morbidity risk among siblings was higher than that for parents. This discrepancy, which is seen in most family studies of schizophrenia, is usually considered to be the result of a selection bias, but in fact it is predicted by the single-locus (and polygenic) model. This is because siblings, unlike any other pair of first-degree relatives, can share *both* genes at a locus through common inheritance.

Matthysse and Kidd applied a different single locus model to published schizophrenia data. The parameters of the model are (1) the frequency of the pathogenic *a* allele (q); (2) the probability of a genetically normal *AA* individual becoming schizophrenic (f_0); (3) the probability of the *Aa* heterozygote becoming schizophrenic (f_1); and (4) the probability of the *aa* homozygote becoming schizophrenic (f_2). When the model was applied to the published data, it predicted an unacceptably low morbidity risk for

monozygotic co-twins of schizophrenics and for offspring of dual schizophrenic matings (both 19.9 percent). However, for the population prevalence, and for siblings and offspring of schizophrenics, a wide range of parameter sets fit the data. The gene frequency varied between 0.3 percent and 2.2 percent, with the f_0, f_1, and f_2 varying from a high of 0.5 percent, 50.5 percent, and 100.0 percent, to a low of 0.0 percent, 19.4 percent, and 38.9 percent respectively. This model also predicted a high rate of sporadic cases (61.2 percent) with 38.7 percent of schizophrenics being heterozygous and 0.1 percent homozygous.

The same investigators tested a multifactorial model based on the following assumptions: (1) a normally distributed population liability to schizophrenia with a mean of 100 and a standard deviation of 15 arbitrary units, (2) a cumulative normal liability distribution representing the probability that a person with a given liability value will develop schizophrenia. The parameters of the model are the liability value resulting in a 50 percent risk and one resulting in a 99 percent risk. When the model was fitted to the data, liability values of 137 and 148 for the two respective parameters gave a good fit to population and first-degree prevalence, but again the model led to unacceptably high risks for monozygotic co-twins (61 percent) and offspring of dual matings (39 percent).

Elston and associates, using Elston's segregation analysis, analyzed a

large sample of two-generation kindreds from Kallman's schizophrenia study. These included 178 pedigrees of probands with "nuclear" schizophrenia and 82 pedigrees of probands with paranoid and simple schizophrenia (the "peripheral" group). The data were analyzed first under a model assuming that probability of being susceptible *(y)* was the same for all genotypes, but, if susceptible, each genotype was characterized by its unique mean age of onset (μ,). The second model assumed that each genotype was characterized by a unique probability of being susceptible *(y),* but that age of onset (ja) was the same for all genotypes. Under each model, the Mendelian *(*$T_{AA.A}$ = 1, $T_{Aa.A}$ = 1/2, $T_{aa.A}$ = 0) and the environmental ($T_{AA.A}$ = $T_{Aa.A}$ = $T_{aa.A}$*)* hypotheses were tested. A trichotomous classification was used in order to include "schizoidia" as affected state 2. Likelihoods were computed for each set of pedigrees under each hypothesis and under the unrestricted "best fit" hypothesis. The results rejected both the genetic and environmental hypotheses in both data sets. However, the parameters of the unrestricted model were quite similar in the nuclear and "peripheral" groups, indicating a similar pattern of transmission in both subtypes.

This analysis differs from the previous single-locus approaches in using segregation analysis rather than fitting parameters of a model to disease prevalences in various classes of relatives. The former approach is a more powerful tool for detecting lack of fit. (The difference between the two approaches can be illustrated with the following example. Assume two

families, each with one affected parent and five children. In the first family, all five children are affected and in the second, none. Taking all children as a group, five of ten are affected, exactly as predicted by autosomal dominance, although in neither family is the segregation ratio close to this expectation.) Perhaps this explains why Elston and Campbell, applying the latter approach to Kallman's data in an earlier analysis, found a good fit to a predominantly recessive single-gene model. The Elston model is a broad one and would subsume most of the early single-gene models (as would the Kidd model), and in addition, his use of "schizoidia" as affected state 2 would subsume Heston's hypothesis as well. Thus, the rejection of the Elston "genetic" hypothesis covers a set of earlier genetic hypotheses. However, it should be remembered that this last analysis was limited to the data from one investigator, and, due to the heterogeneity of the data in this area, the results may not apply to other investigations. It must also be recalled that particular genetic and environmental models were rejected, and the results do not imply that genetics and environment are unimportant in causing schizophrenia.

Affective Disorders

Because of the bipolar-unipolar heterogeneity within affective disorders, early attempts to apply genetic models to affective disorder as a group were doomed to failure. Rosenthal summarized the major hypotheses which included a model with three separate genotypes—two recessive and

one dominant and one postulating an autosomal gene for cyclothymia with an *X* chromosome activating factor to explain the greater incidence in women. With the demonstration that bipolar illness segregates independently of unipolar depression, renewed interest developed in understanding the genetics of affective disorder, particularly the bipolar form.

Of all the genetic models in psychiatry, Winokur's proposal that bipolar illness is transmitted as an X-linked dominant trait has created more controversy than any other. This hypothesis was originally suggested by the finding that there was no father-son transmission in sixty-one bipolar families despite frequent occurrences of other types of parent-offspring transmission. Since the *X* chromosome is transmitted from a father to all daughters but not to sons, this hypothesis accounted for the absence of father-son transmission as well as for the excess of affected females usually observed. In two subsequent studies, Winokur and his colleagues- collected an additional twenty-eight probands and thirty male probands, respectively, again finding virtually no father-son transmission. Other investigators, however, have found frequent instances of father-son transmission in their material, thus contradicting the sex-linkage hypothesis.

A different approach to the question of *X*-linkage is linkage analysis. It is based on the fact that if two genes, a disease gene and a marker gene such as color blindness, lie sufficiently close to one another on the same chromosome,

the frequency of recombination will be less than 0.5 and their assortment within families will not be independent of one another. In practice, the pedigree is identified by a proband with one form of each trait, for example, depression and color blindness (each trait exists in two forms: depressed—not depressed and color blind—not color blind). Relatives who have both forms the same as the proband, or neither form the same, are counted as non-recombinants; those with one form and not the other, as recombinants. For any frequency of recombination *(6),* the probability of encountering the observed number of non-recombinants and recombinants within a family can be calculated from the binomial theorem. The probability at various recombination fractions (θ = 0.0, 0.1, 0.2, 0.3, 0.4) can be compared with the probability under the null hypothesis θ = 0.5 by means of a probability or odds ratio. The odds ratio is usually expressed as the logarithm of the odds (LOD score) and is summed over the pedigrees. If, for any value of *0,* the LOD score reaches 3.0, linkage is considered to be established. Likewise, if the LOD score reaches -2.0, linkage can be considered to be ruled out at that recombination fraction.

Winokur's group first suggested genetic linkage of bipolar illness with the genes for deutan and protan color blindness and the *Xg* blood group. When Mendlewicz and associates added a number of their own kindreds to this material, ten families informative for linkage with deuteranopia yielded a LOD score of 4.50 at a recombination fraction of 0.07, fifteen informative for

protanopia yielded a LOD score of 3.73 at a recombination fraction of 0.10, and twenty-five informative at the *Xg* locus yielded a LOD score of 2.96 at a recombination fraction of 0.19. Thus, linkage was demonstrated at both color blindness loci and strongly suggested at the Xg locus.

These findings have been criticized by Gershon and Bunney, who make the following points regarding linkage work in this area: (1) an association exists in the pedigrees between affective disorder and color blindness that would bias the material toward a finding of linkage; (2) the analytical methods developed for linkage analysis do not allow for such problems as variable age of onset and multiple manifestations of the trait; (3) some of the families are open to alternate interpretations of whether they are informative for linkage; and (4) since the *Xg* and color blindness loci are unlinked, it is unlikely that a third trait would be linked to both. They reanalyzed the data excluding any kindreds they considered to be ambiguous as to informativeness and were unable to support linkage at any of the above three loci. Moreover, Gershon's group has recently studied six new pedigrees informative at the color blindness locus and another six informative at the *Xg* locus. The LOD scores from both these analyses strongly support a verdict of no linkage. At the same time, Mendlewicz and associates have published eight new pedigrees which again support linkage between bipolar illness and the color blindness loci (LOD = 1.55 at $\theta = 0.15$). Mendlewicz found a significant degree of heterogeneity in his material, with some pedigrees supporting

linkage and others not. Indeed, heterogeneity may be the answer to the seemingly endless contradictions in this area.

Since family data from some sources support the A-linkage hypothesis and others contradict it, this would appear to be a promising area for the application of genetic models and indeed a number of approaches have been tried.

Several studies have used Slater's computational model to analyze bipolar families. In twenty-six kindreds, Slater and associates found a unilateral to bilateral ratio of affected pairs of relatives of 38 to 30, which was consistent with the polygenic expectation of 2 to 1. In his large family study, Perris examined twenty bipolar and eight unipolar kindreds. The bipolar ratio was 46 to 15 and the unipolar one 12 to 8, both consistent with polygenic transmission. Mendlewicz and associates separated out their bipolar families containing a first-degree relative with bipolar illness, and among these relatives the unilateral to bilateral ratio was 42 to 6, significantly favoring a single gene. The different result may be due to a different method of selecting the pedigrees for analysis. Whatever the reason, this was the only result consistent with a single gene, X-linked or not.

Crowe and Smouse performed a pedigree analysis on Winokur's original sixty-one kindreds, which had initiated the sex-linkage hypothesis. An age-

correction was introduced and used to calculate the expected numbers of ill relatives under both the sex-linked dominant (SLD) and the autosomal dominant (AD) hypotheses. A likelihood test of fit was used, and both models provided a satisfactory fit, with the SLD hypothesis fitting somewhat better *(p* > 0.75) than the AD *(p* > 0.10). When the models were compared, the sex-linkage hypothesis was favored with an odds ratio of 89 to 1, although the ratio was not statistically significant.

Bipolar illness is suitable for analysis by multiple threshold models, with the bipolar form representing the narrow threshold and the category of bipolar and unipolar illness defining the broad threshold. Gershon's group has analyzed the published data along these lines. In addition to the two thresholds already discussed, they defined a third one to include "related" affective disorders such as mild depressions and cyclothymia. The single-locus model is now defined by the following parameters: (1) gene frequency (*q*); (2) environmental variance (e); (3) dominance (*h*'); (4) threshold for major affective disorders *(T);* (5) bipolar threshold (T_{Bp}); and (6) in the case of the three-threshold model, threshold for related disorders *(T_{Rel}).* With two thresholds, there are fourteen independent observations; with three thresholds, twenty, leaving nine and fourteen degrees of freedom to test the respective models.

In the multifactorial model, dominance variance (stronger correlations

between siblings than between parents and offspring due to the fact that siblings can share in common both genes at a locus through common inheritance) can be dealt with by computing the parent-offspring and sib-sib correlations separately. If three thresholds are used, this leads to five parameters: three population prevalences and two correlations; in the case of two thresholds, there will be four parameters. With two thresholds, there are fourteen independent observations and with three thresholds, twenty, leaving ten and fifteen degrees of freedom respectively to test each model.

When the four models were applied to Gershon's data, every model gave a satisfactory fit. Taking the multifactorial models first, the two-threshold approximation gave a best-fitting parameter set *(p* > 0.3), which estimated the population prevalence of all affective disorder (bipolar plus unipolar, or *BP + UP)* at 1.8 percent and bipolar illness at 0.4 percent. The sib-sib and parent-offspring correlations were, respectively, 0.37 and 0.31, indicating little or no dominance effect. The three-threshold solution yielded the following population prevalences *(p* > .05): all affective disorder, 3.1 percent; bipolar plus unipolar, 1.6 percent; and bipolar alone, 0.4 percent. The sib-sib and parent-offspring correlations were 0.35 and 0.39, respectively. Thus, both models predicted a relatively common disorder that is strongly familial and no evidence of a dominance effect was found.

Of the two single-locus models, the two-threshold one gave the better fit

(p > 0.5) and estimated the gene frequency (*q*) at 0.21 and the variance (e) at 0.14, making the standard deviation *(e)* 0.37. The *a* allele was completely recessive *(h′* = 0), positioning the *Aa* mean at o with the *AA* mean. The threshold for major affective disorder (*T)* was positioned at 2.1 and that for bipolar affective disorder (T_{Bp}) at 2.43. These thresholds are 5.7 and 6.6 S.D., respectively, above the *AA* and *Aa* means, making it highly unlikely that a person with either genotype would ever develop affective disorder. Therefore, the model predicts a common completely recessive gene with most affected persons being homozygous recessive but with 33 percent [2*q* (1 — *q*)] of the population being heterozygous carriers. The three-threshold approximation fit less well *(p* > 0.1) with the following parameter estimates: *q* = 0.045, ϵ^2 = 0.28, *h′* = 1.4, T_{Rel} = 1.7, *T* =1.9, T_{Bp} = 2.3. This solution predicts a less frequent gene with moderate dominance such that a substantial portion of the *Aa* liability distribution exceeds the thresholds. Here it is apparent that differences in the beginning assumptions of a model can lead to major differences in what the model predicts about the mode of transmission.

Gershon and associates analyzed the data from Angst's and Perris's studies in a like manner using two categories of affected: bipolar and bipolar plus unipolar. Angst's data fit both models but Perris's rejected both the multifactorial and the single-locus models. For the multifactorial model, the best-fitting parameter set *(p* > 0.05) for Angst's data gave a population prevalence of 0.4 percent for major affective disorder and 0.03 percent for

bipolar illness. The respective parent-offspring and sib-sib correlations were 0.43 and 0.47, indicating a strongly familial trait but little or no dominance effect. The single-locus model predicted the following parameter set ($p > 0.05$): $q = 0.06$, $\epsilon^2 = 0.45$, $h' = 0.34$, $T = 1.2$, and $T_{Bp} = 2.3$.

Bipolar illness may also be analyzed with respect to sex thresholds, since most studies find females more frequently affected than males, the ratio being approximately 1.5 to 1. Gershon's group applied the single-locus and multifactorial models with sex thresholds (T_m and T_f) to five studies: those of Winokur and associates Mendlewicz and Rainer, Goetzl and associates, James and Chapman, and Gershon and associates. Both the single-locus and the multifactorial models fit the last three studies, but both were rejected by the first two. The three studies fitting the models were then analyzed by the same models without sex thresholds ($T_m = T_f$), and only James's data rejected the models. Because of the question of X-linkage, an X-chromosome dominant model was tested on the data of Winokur and those of Mendlewicz, the two studies suggestive of X-linkage. The model fit Winokur's data but was rejected by those of Mendlewicz. Thus, two studies rejected sex threshold models as an explanation for the sex differences in prevalence but only one of these was compatible with a sex-linkage explanation. Three studies were compatible with sex thresholds but in only one of these were they necessary to account for the observations.

What can be concluded from these studies? Regarding the question of sex linkage, the data that originally suggested the hypothesis have been rigorously tested and continue to support it. However, the majority of family studies do not suggest sex linkage, and unfortunately, in these the multifactorial and single-locus models have been equally satisfactory, with studies that reject one rejecting both. The analyses have demonstrated that a sex-linkage hypothesis is not necessary to account for the sex prevalence differences. Finally, the fact that different data sets lead to very different conclusions, not only in model but also in parameters of the model, speaks for the considerable degree of heterogeneity among studies in this area.

Antisocial Personality and Hysteria

Since there is considerable evidence from adoption studies for a genetic predisposition to antisocial personality, and since antisocial personality and hysteria are typically seen together in families, these disorders provide an ideal situation for analysis by transmission models. The problem requires the use of thresholds for both sex and severity.

The relevant observations are the following: The population prevalence of antisocial personality in males is considerably greater than the female prevalence, and hysteria is found almost exclusively in females. Likewise, among the relatives of male and female anti-socials and hysteric women,

antisocial personality is found more frequently in males than females and hysteria is found exclusively in females. These observations suggest a model with different thresholds for antisocial personality in males and females, with the female threshold representing a more extreme deviation from the mean. In women, hysteria may be viewed as a milder form of antisocial personality, such that antisocial personality represents the narrow threshold and hysteria plus antisocial personality the broad threshold. Thus, males have a wide threshold for antisocial personality and females a narrow threshold for antisocial personality and a wide threshold for hysteria.

Cloninger and associates- applied the multifactorial multiple threshold model to their data on antisocial personality and hysteria. The model was first tested on the data on antisocial personality. These were prevalences of antisocial personality in male and female relatives of both male and female anti-socials and the population prevalences of both sexes. These six sets of observations were used to obtain the best-fitting set of three parameters: population prevalence in males and females, and correlation between first-degree relatives. The multifactorial model provided a close fit to the data *($p >$* 0.9). Among personally interviewed first-degree relatives of white anti-socials, the expected population prevalences were 3.6 percent for men and 0.7 percent for women. The first-degree relative correlation of 0.55 indicated strong familial transmission.

When the model is expanded to include hysteria it yields a set of twelve observations: the prevalence of antisocial men, antisocial women, and hysteric women in the general population and in first-degree relatives of each of these three classes of affected subjects. These twelve observations determine a best-fitting set of four parameters: population prevalences of antisocial men, antisocial women, hysteric women, and the correlation between relatives; leaving eight degrees of freedom for testing the minimum chi-square. When the model was compared to the data it provided a close fit *(p* > 0.4), estimating population prevalences of 3.8 percent for antisocial men, 0.5 percent for antisocial women, and 3.0 percent for hysteric women. The correlation between first-degree relatives was 0.54.

The results indicate that the multifactorial threshold model provides a very satisfactory explanation for the data on the familial transmission of antisocial personality and hysteria. Moreover, including hysteria in the analysis leads to an acceptable fit without substantially changing the parameters predicted from antisocial personality alone, providing further evidence that these disorders may be alternate forms of the same process. This was the first example of a genetic model providing a unitary hypothesis explaining the coincidence of two distinct diseases.

The same group used multifactorial models to test hypotheses about sex differences in the prevalence of antisocial personality. The appropriate

models are the three modifications of the Reich multifactorial threshold model: the isocorrelational model, the environmental model, and the independent model. The isocorrelational model predicts that extrafamilial factors affecting liability affect the two sexes equally. As a result, all four correlations among relatives (male-male, male-female, female-female, female-male) are equal. The model is tested with six sets of observations: the population prevalence in each sex plus the prevalence in each sex of relative of each sex proband; and is defined by three parameters: male population prevalence, female population prevalence, and correlation among relatives, leaving three degrees of freedom to test the chi-square. Since the model fit the data on antisocial personality very closely *(p* > 0.9), it explained the data without invoking extrafamilial factors that preferentially affect one sex, and testing the environmental or independent models became unnecessary.

Alcoholism

Alcoholism is more prevalent in men than in women and, therefore, may be analyzed with multiple threshold models in the same manner as antisocial personality. Cloninger and associates analyzed a series of pedigrees from their center and found that the isocorrelational model did not lead to a good fit *(p* > 0.05). Thus, it became necessary to test the environmental model. This model predicts that extrafamilial factors that contribute to liability act preferentially on one sex. This is reflected mathematically in the correlation

between females being unequal to the correlation between males. Thus, the model is defined by four parameters: the population prevalence in males and in females, the male-male correlation, and the female-female correlation. Six sets of observations are possible: the population prevalence of each sex, and the first-degree relative prevalence in each sex of each sex proband, leaving two degrees of freedom for testing the best-fitting chi-square. When this model was applied to the data, the fit was very good *($p > 0.8$)*. The female-female correlation was estimated at 0.18 ± 0.12, significantly lower than the male-male correlation of 0.53 ± 0.07, and consistent with the hypothesis of extrafamilial factors acting preferentially in women.

The isocorrelational and environmental models are based on the assumption that the same familial factors are relevant to the etiology of the trait in both sexes. If familial etiologic factors in one sex are only partly correlated with those factors in the other sex, then sex differences occur due to the partial independence of these factors. This is reflected mathematically in a reduced correlation between opposite sexes (male-female, female-male) from the expected geometric mean of the two same-sex correlations. This can be expressed mathematically by the phenotypic correlation *(r_p): $r_P = r_{mf}/(r_{mm}$ $r_{ff})1/2$* and $r_P = r_{fm}/(r_{mm}r_{ff})^{1/2}$. If r_P is significantly less than 1, the environmental model is rejected and the independent model is accepted. The data on alcoholism estimated $r_P = 0.94 \pm 0.33$, providing no basis for invoking the independent model.

This set of analyses indicates that the sex differences in alcoholism are compatible with a hypothesis of extrafamilial liability factors acting preferentially on the female but with familial factors being equally important in the two sexes. This set of circumstances might occur, for example, if alcoholism were equally hereditary in both sexes but social pressures made women less likely to drink.

Panic Disorder

The high familial prevalence of panic disorder makes it a good candidate for transmission models. A series of nineteen carefully studied kindreds have recently been analyzed.- First, the Slater computational model was applied to fifteen informative kindreds with the finding of a unilateral to bilateral ratio of 43 to 4, in contrast to the expected one of 31 to 16. The result was highly significant *(p* < 0.001) in favor of the single gene hypothesis.

The data were then analyzed by the Elston segregation analysis model with the Mendelian hypothesis providing an acceptable fit *(p* > 0.1). The environmental hypothesis was rejected at a highly significant level *(p* < 001). The best-fitting Mendelian hypothesis predicted an *A* allele frequency (*q)* of 0.014, leading to 4.2 percent of the population having the *A* allele in either homozygous *(AA)* or heterozygous *(Aa)* form [q^2 + 2*q(*1 - 9)]. The susceptibility parameter *(y)* estimated 75 percent of the population to be

susceptible regardless of genotype, but the age of onset distribution of the more frequent *aa* genotype ($\mu = 5.9, y = 0.22$) effectively ruled out their ever being affected. The mean age of onset for the *AA* and *Aa* genotypes was twenty-two years with a 2 S.D. range of eighteen to thirty-four. Thus, the model assumes a gene present in 4.2 percent of the population, with 75 percent of the carriers being susceptible and their age of onset distribution being such that 95 percent are affected by age thirty-four.

Conclusion

In conclusion, what have transmission models contributed to the field of psychiatry? It is apparent from the foregoing review that they have not answered the basic question of how any mental illness is inherited. However, in fairness, it is probably asking too much, in our present state of knowledge, to expect this kind of conclusion from them. As long as psychiatric data sets contain the kind of diagnostic heterogeneity that has recently been demonstrated in affective disorders, one can hardly expect firm conclusions about the mode of inheritance. Thus, if the models have not lived up to the promise of clarifying inheritance, this may be because our present mathematical sophistication exceeds our diagnostic sophistication. Nevertheless, transmission models have been influential in modifying traditional ways of thinking about the manner in which genes and environment can cause disease. Modern concepts of disease transmission

have come a long way from the simplistic Mendelian concepts of a generation ago. When our diagnostic abilities succeed in rivaling our mathematical ones, the means exist for learning much about disease transmission.

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Notes

1This term refers to genetic variance that can be transmitted to progeny. Siblings can share two genes at a locus through common inheritance, creating "dominance" variance that cannot be

transmitted since only one gene is passed to offspring. Thus, $V_G = V_A + V_D$, where V_A and V_D refer to additive and dominance variance, respectively. Heritability based on additive genetic variance ($h^2 = V_A/V_T$) is referred to as heritability in the "narrow" sense and that based on total genetic variance ($h^2 = V_G/V_T$) is heritability in the "broad" sense. (For a complete treatment of this subject, see reference 15.)h2

2See footnote to figure 4-1 regarding notation.