Archives of General Psychiatry,
1989, *46*, 935–944.

Schizotaxia Revisited

Paul E. Meehl, PhD

• A conjectured neural integrative defect (schizotaxia), due to a dominant schizogene completely penetrant for a parametric aberration in synaptic signal selectivity (hypokrisia), gives rise under ordinary social learning regimes to schizotypy, a personality showing ambivalence, aversive drift, dereism, autism, and cognitive slippage. Given unfavorable polygenic potentiators (eg, introversion, hypohedonia, and anxiety) and adverse life experiences (eg, childhood trauma or adult misfortune), around 10% develop schizophrenia. That schizophrenia is basically a neurologic disorder does not contradict whatever is known about its psychodynamics, nor preclude efficacy for psychotherapy or other psychosocial interventions. Research should concentrate on soft neurology and psychophysiology as indicators, being closer in the causal chain to the schizogene than psychometric, social, or high-level cognitive processes. Taxometric statistics are appropriate to testing a major locus model not simplistically formulated.

(*Arch Gen Psychiatry.* 1989;46:935-944)

Over a quarter century ago, in my presidential address to the American Psychological Association,[1] I began by pointing out that the only nonsymptom, nonpsychometric fact you can know about a person that gives you better than an even chance in a wager that the person will develop schizophrenia is that his or her monozygotic twin is schizophrenic. I concluded that lecture by predicting that when suitable indicators with appropriate taxonomic statistics were applied, it would become clear that schizophrenia is a neurologic disorder of genetic origin. By the term *schizotaxia, a* neologism in the title of the lecture, I designated a neural integrative defect that I conjectured to be the basic pathophysiology of the disorder, upon which, by the usual processes of social learning, there develops a personality structure I called, following Rado[2,3] and Rado and Daniels,[4] the schizotype.[5] I also conjectured, again following Rado, that only a minority of schizotypal individuals decompensate into a clinical schizophrenia. These views were heretical among psychiatrists and, probably even more, among clinical psychologists in 1962, but are increasingly accepted today by informed scholars and practitioners. Radical environmentalism was ubiquitous in those days, and the somatic phenomena of schizophrenia, known since the classic works of Kraepelin[6] and Bleuler,[7,8] were either ignored or presumed to be psychosomatic in origin. It is to the merit of Fish[9-12] to have revived these issues in her important developmental studies. The excellent book by Dollard and Miller[13] on personality and psychotherapy, in which they offered a Hullian reconstruction of psychoanalytic concepts about mental disorder and treatment, does not contain a single index reference to the terms *gene, constitution,* or *heredity,* and these able authors were writing in harmony with the then-dominant theoretical tradition. In the decade following World War II, the only probable deviator from the received psychodynamic, family pattern, schizophrenogenic mother theory would have been the medical director of a state hospital in the Midwest, of an older generation. Such a psychiatrist (I knew several) would consider schizophrenia in some sense "organic," although I do not recall any going so far as to call it "neurologic." Since I turn out to have been a fairly good minority report prophet, I am pleased at the invitation of Dr Freedman to offer a brief statement of my current views, and I shall in the course of so doing permit myself to be somewhat personal, referring to influences on me as a scientist and clinical practitioner, again at Dr Freedman's urging.

I cannot say exactly when I began to adopt a strong genetic view as to the specific etiology of schizophrenia, but it must have been around the end of World War II. I recall heated debates as a first-year graduate student (1941-1942) with a fellow teaching assistant, Lloyd George Everest, in which I took a psychodynamic and social learning view of the etiology of schizophrenia and he argued for an organic interpretation. He told me of a study showing that tadpoles die swimming in schizophrenic blood plasma, and he referred me to the twin studies by psychiatrist Rosanoff and colleagues[14] on the genetics of manic depression and schizophrenia. Lecture notes of students who took my beginning clinical psychology course in 1946 indicate that while I said that the etiology of schizophrenia was unknown, I did tell them about some of the soft neurologic signs, the Worcester group's data on vestibular nystagmus,[15-18] the reduction in the specific dynamic action of protein,[19] and the vascular and muscular differences between the schizophrenic subtypes found post mortem,[20] trends presumably related to Sheldon's distinction between the "mesomorphic toughness" of paranoids and the ectomorphic "hebephrenic jettisoning."[21] I do not know when I first read Kallmann's classic 1946 twin study,[22] but my colleague Lloyd Sines, PhD, says that in the fall of 1952, he was exposed, he is certain by me, to the idea that "insanity is in the blood." I am confident that by the early 1950s I had adopted a strong genetic and neurologic theory about schizophrenia, approximately a decade before my American Psychological Association speech.

While I came into psychology from reading Menninger's *The Human Mind* and hence with a strong Freudian orientation, the Minnesota department was

Accepted for publication November 23, 1988.
From the Department of Psychiatry, Psychiatry Research Unit, University of Minnesota, Minneapolis.
[Text page numbers do not correspond exactly with original publication.]

definitely not psychoanalytic. My doctoral adviser, Starke Hathaway, PhD, was strongly anti-Freudian. Animal psychologist William T. Heron did early work on the inheritance of maze learning ability and activity level in the rat. My undergraduate adviser, Donald G. Paterson, emphasized the hereditary factors in intelligence in his class on individual differences. As to the "soft neurology" of schizophrenia,[23] I recall vividly a case conference when the psychiatry department head, J. Charnley McKinley, MD, PhD, an old-style "neuropsychiatrist" who always did at least a basic neurologic examination on psychiatric patients, elicited a fairly striking dysdiadochokinesia with no other signs of neurologic disease in a patient who was clinically and psycho-metrically an obvious schizophrene. McKinley warned the medical students that they should be careful not to jump to the conclusion, when some body had a plus/minus dysdiadochokinesia, or past pointing, or even a positive Romberg sign, that there was neurologic disease in the cerebellum or dorsal columns. He said that for some unknown reason, a sizable minority of schizophrenes showed these kinds of phenomena. I recall, when I was giving colloquia around the country in the late 1940s about the Minnesota Multiphasic Personality Inventory (MMPI), being asked how I explained the eight neurologic items on the Sc scale, which I had some trouble doing. I simply pointed out that the test was developed empirically, and if a theory of schizophrenia did not explain the fact, then there was something wrong with the theory. (One must remember that Bleuler's 1911 book was for some strange reason not published in English until 1950!) In the middle 1950s, my analyst and subsequent analytic supervisor, Bernard C. Glueck, Jr, MD, who was trained under Rado at the Columbia Psychoanalytic Clinic, led me while still his analysand to read Rado, and the classic article by Hoch and Polatin[24] on pseudo-neurotic schizophrenia (which was followed some years later by an outcome study[25]). In Rado I came across the theory that the basis for schizotypy was a hereditary combination of kinesthetic diathesis and hedonic defect. In terms of Rado's concept of the action self and the formation of the ego as a getter of pleasure, this interactive combination of a proprioceptive and pleasure impairment was an interesting theory and one that even now I do not consider can be rejected as without merit.

Meanwhile, I was engaging in psychotherapy and had occasion to contrast the behavior of my schizotypal and neurotic patients. I treated my first patient in 1942 with a combination of cognitive therapy and behavior modification, and looking back I believe that he was a schizotype, although at the time I diagnosed him as severely obsessive-compulsive. Due to intellectual influences mentioned, my experience as a practitioner did not lead me to emphasize family dynamics or the schizophrenogenic mother. On the contrary, the more I worked with these patients the more I became convinced that there was something radically wrong with their central nervous systems (CNSs). I am reminded that Carl Rogers, despite his antinosologic bent (which even considered making a diagnosis to be counterproductive for the psychological helper), told me in the early 1960s that his work with schizophrenes at the University of Wisconsin led him to suspect that "these people have something wrong with their brains." Therapeutic experience did not lead me to throw out what we know about the psychodynamics of schizophrenia, although it seemed quite clear to me that Freud was wrong in saying that they do not form a transference. I remain persuaded to this day that a sufficiently flexible and active approach can help keep a schizotype compensated, although I can present no quantitative evidence to that effect. Of course, what the practice of psychotherapy does to one's views depends a lot on prior theoretical predilections, and what one elicits and remembers from therapy sessions is unavoidably slanted. For example, when I became interested in the soft neurology business and began to formulate a theory of schizophrenia around 1955, I found myself noticing how many schizotypal patients spontaneously reported that when they were small children they did not seem to be having as much fun as the other kids even when they did not experience rejection or anxiety (Rado's anhedonia) and how many of them spontaneously reported being motorically clumsy, being known as the "klutz" of the family, and the like. It is interesting that the best single indicator of the motor impairment of schizophrenes has been found to be a globally evaluated "general clumsiness."[26]

THEORETICAL AND METHODOLOGIC STRATEGY

I will not go into the respects in which I think my 1962 position erred and why, because I am preparing a longer article for another place, and will here simply set out today's version. In constructing a conjectured general theory of schizophrenia, the first thing to do is try looking at the phenomena as though they were not so familiar to us. Both psychiatrists and psychologists tend to have read and heard about the syndrome before they become theorists and practitioners, many of us already as sophomores in a general psychology class, which leads us to take for granted the going-together of some things that, looked at freshly and naively, do not seem to have any reason to appear together. In this respect, schizophrenia differs from the affective disorders, for which even a layman could probably give a pretty good description of being "up" or "down" without ever having seen a diagnosable case. This qualitative diversity of the symptomatology gives the theoretical tip-off, namely, if there is something a little bit haywire about almost every level and sector of the patient's functioning, a sensible theoretical strategy is to conjecture that there is something wrong with the CNS throughout. So my conjecture about the neural integrative defect of schizotaxia is that it is ubiquitous, that it is something wrong with every single nerve cell at all levels from the sacral cord to the frontal lobes.

The usual theoretical strategy proceeds differently by selecting some clinically striking or socially important aspect of the syndrome and identifying it with a particular psychological function or brain region or biochemistry, which is then considered the specific pathology. The obvious problem with this approach comes when the theorist has to deal with the other facets of the syndrome. He has to do some fancy footwork, complicated ad hoeing, and procrustean forcing to get an explanation of these noncentral items, as a result of which other theorists do not find his effort persuasive. The family dynamics view that was prevalent around World War II seemed to do a somewhat better job of this because the clinical focus was on the interpersonal abnormalities. However, it did not do a good job with the grave cognitive defects, and in effect ignored the soft neurology and psychophysiology. To stay away from contemporary theories, I give a couple of examples from the 1940s, when I was a

psychology intern at the University of Minnesota Hospitals. Starting with the alleged efficacy of insulin treatment and the fact that the brain cells cannot use anything but carbohydrates, and maybe some such anecdotal observations as that many schizophrenes like to gobble sweets (Hitler!), it was conjectured that the specific pathology of schizophrenia was something aberrant in the carbohydrate metabolism. Or again, the "reticular activating system" having first been discovered in the late 1930s, looking at catatonic raptus or the withdrawn mute catatonic and the low activity level of late-stage chronic schizophrenias, it seemed reasonable to think that there was something wrong with the reticular activating system. However, that did not do much for us by way of understanding the social aversiveness, the cognitive slippage, and the like.

Since my theoretical strategy starts by postulating a ubiquitous malfunction, it has the opposite problem from these other theories, namely, it has to explain why different functions are not equally impaired. But this is a theoretical advantage methodologically, as we do not have nearly as much necessity for ad hocery and procrustean forcing. Why? Because we already know from the classical psychometric model of group factors and specifics, and from the well-established fact of individual differences in many domains outside of pathology, that the presence of a general factor should not lead us to expect it to operate equally in all domains. For example, the general intelligence factor permeates all the subtests of an omnibus intelligence test, but nobody expects that factor to have equal factor loadings on the subtests, and we find that it does not. So the situation with regard to ad hoc assumptions and procrustean forcing is much better with my kind of theory because one does not have to invent afresh the kinds of theoretical influences that lead to some levels or sectors being relatively more aberrant than others. It should also be remembered that we have no clear-cut metric for degree of impairment in different behavior sectors unless all functions studied are quantified in standard score units. Lacking this, it is natural for practitioners to perceive that the grossest impairment in schizophrenia is in interpersonal relations, and it is of course the most important from the standpoint of other persons (family, coworkers, and the larger society). After all, nobody cares very much whether a person has trouble visually tracking the sinusoidal target, and nobody but a neurologist will notice if one has a marginal dysdiadochokinesia. There are some general considerations, based on a neural integrative defect theory treated in the way we do classic psychometrics, that give plausible leads as to which kinds of functions one might reasonably expect to be more deviant, and I have explained them elsewhere.[27]

Another piece of strategic advice is that one ought not to be afraid of mixing explanatory levels. The phenomena of catatonic negativism cannot be "explained" in a nonpsychological way, that is, by some kind of simple neurologizing of opposed movements in the musculature, because as Bleuler pointed out 70 years ago, there is a molar, purposive aspect to catatonic negativism; as, for instance, such superficially opposite things as mutism and echolalia, or negativism and command automatism, have the common characteristic to minimize the psychological stress of dealing with the social environment's demands. However, it would be equally foolish to try to explain past pointing or dysdiadochokinesia on social or psychodynamic grounds. One problem here is that, even today, most clinicians do not fully accept the thesis that the mind is the brain in action, so that the schizotaxic defect may be expected to manifest itself quite directly in influencing, say, something like postrotatory nystagmus or the P50 evoked potential anomaly,[28] but that same basic defect will presumably influence verbal aberrations or social withdrawal or impaired pleasure only in a more indirect way, one in which the social learning history plays a basic part. The early schizophrene's delusion of the end of the world is probably a symbolic, intellectualized expression of his awareness of withdrawn cathexis from the inner representations of social objects—a psychodynamic account of symptom formation. However, some of the semantic or perceptual aberrations in its form and content may be more directly attributable to the primary cognitive slippage, via the schizotaxic defect itself. I have discussed this levels-of-analysis problem and the unavoidability of moving up and down in them elsewhere.[27,29]

It is also essential to my approach that taxonic models are causally and statistically different in important respects from nontaxonic (dimensional, factorial) models. For example, in classic psychometrics, we want the indicators of a latent factor to be highly correlated, whereas the ideal situation in taxometric detection of a categorical entity is that there should be negligible "nuisance correlation," so that the observed manifest relationship between two fallible indicators of the same latent taxon will be almost wholly due to their taxonic validity and not to the influence of quantitative factors.[30-33] A particularly useful taxometric result is that the statistical patterns of only moderately valid fallible indicators permit estimates of higher validity for another indicator, the extreme case of this "bootstrapsing" being one in which the weak signs enable one to detect that a new sign is infallible, the Super-Bootstraps Theorem.[27,30,33]

It is odd that some psychologists dislike my kind of theory as being identified with the "medical model" (clearly my intention), whereas both psychiatrists and psychologists, whether favorable or unfavorable toward *DSM-III,* usually view the latter as an implementation of the medical model. I think this is a conceptual mistake. The authors of *DSM-III* tried hard to be descriptive-phenomenological (because the committees could not realistically aim for agreement as to pathology or etiology), so the resulting nosologic rubrics bear more resemblance to a pre-Virchow listing of "kinds of fevers"[34] than they do to the list of kinds of "anemia" found in a chapter of Harrison's *Internal Medicine.* The modern medical model identifies entities by the joint criteria of their pathology and etiology, not by their syndromic clustering. I am not faulting the constructors of *DSM-III* or opposing the use of it as an instrument in descriptive psychiatry; that is definitely not my position. I am merely pointing out that to identify these phenomenological rubrics as closely analogous to the disease entities of other branches of medicine is methodologically misleading. The literal "operational definition" of a disease entity by the conjunctive and disjunctive criteria of *DSM-III* is forced on us in the absence of satisfactory agreement about pathology and etiology, and is *at this time* the best we can do if we want to make reliable diagnoses in psychopathology. However, it ignores the latent-manifest distinction, and the fact that in the life sciences, the connection between the latent state of affairs and the manifest indicators is almost always stochastic. There are few diagnostic signs even in

organic medicine that are two-way pathognomonic, presenting no false-positives and no false-negatives (in the language of the epidemiologist, perfect sensitivity and perfect specificity). The latent-manifest distinction is not something peculiar to psychodynamics of the kind that many younger psychiatrists view with skepticism. It is also clearly set out in such more scientifically accepted fields as genetics, the classical psychometric model of factor analysis, and the theories of latent learning in experimental psychology and animal behavior.[35]

I sometimes think that we psychologists have brainwashed our psychiatric brethren into an obsession with reliability, without sophisticating them sufficiently about the relationship between reliability and net attenuated construct validity.[35,36] The reliability coefficient does set an upper bound on validity, but in the first place, it is the square root that is the bound; and in the second place, in the behavioral sciences and much of the biological sciences, that upper bound is so far above the validity coefficient that one cannot infer mathematically whether revising an indicator, or substituting one indicator for another with lower reliability, will raise or lower the validity. Dr Hathaway, codeveloper with Dr McKinley of the MMPI and certainly no muddle-headed acceptor of unreliable clinical observations and inferences, emphasized this simple point by an example from nonpsychiatric medicine. Whatever a patient's presenting complaint, the physician regularly takes the patient's blood pressure, and a physician who performed a physical examination without taking blood pressure could surely be faulted. Yet the reliability of blood pressure readings, both because of diurnal variability and interjudge differences in procedure, is rather poor. I have seen reliability coefficients as low as $r = .65$ for blood pressure determinations. The width of the wrist can be measured by anthropometric instruments with a reliability in the high .90 range. Why then does a physician regularly measure blood pressure and never (unless thinking about acromegaly...) measure the wrist width? The answer of course is that blood pressure is such an intrinsically valid sign of important medical conditions that we insist on measuring it, even if unreliably, whereas the diagnostic validity of wrist width is negligible. For example, I like to include Bleuler's ambivalence as a core feature of schizotypy, but one does not find it in *DSM-III* or the Schedule for Affective Disorders and Schizophrenia, mainly, I suspect, because it cannot be reliably assessed in brief, nontherapeutic study of the patient.

THE SCHIZOTAXIA THEORY

I have been asked why we need two different words, *schizotaxia* and *schizotypy,* if all the persons who have one have the other. What I said in 1962 was that all schizotaxics become schizotypal *on all actual reinforcement schedules,* and that latter was not empty phraseology. My point was that the schizotaxic paramters of the brain lead, in the ordinary range of social reinforcement schedules (provided by the primary care-iver and subsequently by siblings, peers, teachrs, etc), to development of a schizotypal personality organization. However, one should leave open the possibility that a sufficiently well-managed prophylaxis, given diagnosis of an infant as schizotaxic, might prevent at least portions of this organization from developing. One wants to leave such things open as empirical questions and not prejudge them definitionally. Furthermore, a one-to-one correlation over individuals between two things does not mean that the two things are conceptually identical. To use logician Willard Van Orman Quine's favorite example, all animals with a heart have a kidney, but that does not show that the words *heart* and *kidney* designate the same concept!

Of course, schizotaxia defined simply as an integrative neural deficit is a pretty vague notion, so I tell our clinical students that if they want to think in a sophisticated way about this kind of theorizing they should read philosopher Arthur Pap on open concepts.[37-40(pp21,195)] On the other hand, it is not completely vague. One specifies, for example, that it is a defect not of input, or storage, or retrieval, as in a memory defect or mental deficiency; and it is not among the integrative defects producing dyslexia, tone deafness, the hereditary spelling defect, or garden variety poor motor skills; but it is an integrative deficit predisposing to schizophrenia, and of genetic origin. Such an open concept is defined contextually (or "implicitly," as the logicians would have it). Its meaning is given mainly by its role in the network of antecedents, eg, in my theory a dominant gene, and in its consequences, eg, the psychophysiology, soft neurology, semantic aberrations, other forms of cognitive slippage, and the like. If you fill in the intrinsic content you have to talk in neurologic terms rather than in terms of the molar-defined causal network.[27,41]

One may accept the concept of schizotaxia as an integrative deficit defined contextually but may be unwilling to accept the more specific filling-in that I offer with the concept *hypokrisia.* One does not solve scientific problems by making up words, but it is necessary to have a word to refer to a concept if another is not available. The conjectured hypokrisia (from the Greek words meaning an insufficient differentiation or discrimination) I take today, as I did in my 1962 lecture, to refer to a slight quantitative aberration in the synaptic control over the spiking of a neuron. Neglecting non-spike transmission, which we did not know about in 1962, the conjecture is as follows: considering all of the terminal buttons over a cell's synaptic scale and coordinating each one with an axis (thus defining the synaptic signal space), a given spatiotemporal pattern of arrivals of presynaptic impulses over the synaptic scale defines a point in the space, if the arrival times from an arbitrary zero point are associated with each of the coordinates. Associated with this point is, for a resting condition of the cell not in refractory phase, a certain Lorente de No optional transmission probability of spiking. The hypersurface of these probabilities represents the likelihood that any given spatiotemporal pattern of stimulation will produce a spike. The hypokrisia conjecture says that this hypersurface is (1) elevated and (2) dedifferentiated, ie, has a flattening of its hills and valleys in the schizotaxic brain when compared with the orthotaxic. From this simple ubiquitous defect I attempt to derive not all (that would be absurd) but most of the important phenomena of schizotaxia and its personality resultant, schizotypy.

If pressed further as to the defect, one might conjecture either an anomalous distribution microanatomically over the synaptic scale, or, as I prefer, a deficient biochemical substance *x* whose specific function in the normal brain is to retard the spread of regions of depolarization under each synaptic knob, or to facilitate repolarization, thereby lowering the odds that a given pattern of inputs will be over spike

threshold. On this basis I conjecture that there will be parametric alterations in the control functions linking one Hebbian cell assembly[42] or, as today we would say, one module or system of modules to another. How much impact this kind of quantitative aberration will have on various functions will involve parametric relations in structural features that it is premature to speculate about, given our generally imperfect knowledge of how the brain works, except in the rough kind of relation mentioned above as to which broad classes of functions might be expected to be more aberrated.

An alternative neurophysiology theory of what underlies molar schizotaxia[1] postulates a generalized quantitative deficiency of CNS inhibitory function. This interpretation of the integrative defect is the one preferred by Freedman and his colleagues,[28] and it does seem a natural interpretation of the P50 anomaly, that being a failure in schizophrenes to prevent or dampen the second cortical evoked response, as normally occurs. The phenomenology of early schizophrenia, which often includes complaints of "stimulus overload," distractibility, difficulty in maintaining focus, exaggerated startle, etc, is also consistent with a deficient inhibition concept.[43] On the other side, some impairments described so well by Bleuler could look like excessive inhibition, as does full-blown catatonic withdrawal. The interpretive problem here is, again, our relative ignorance of normal CNS integrative processes, especially as to the parametrics of their convergence and feedback features. (One thinks of the paradoxical benefits of methylphenidate hydrochloride on the hyperactive child.) In our relative ignorance of details about cerebral systems in their hierarchical and convergent control relations, we are rather like someone considering a nonlinear, multiple-output Rube Goldberg machine, wondering whether its quantitatively aberrant outputs can best be explained by *more* or *less* friction ("play" or "binding") at each link between moving parts. So while I am tentatively pushing hypokrisia as the core defect, the inhibitory deficiency alternative is surely an option worth testing. Whenever we find domain variations in intensity or direction of effects, there is of course a considerable explanatory symmetry between "overexcitation" and "underinhibition," difficult to resolve without more knowledge of how the whole system works.

As to the affective, motivational, and interpersonal deviations, I hold essentially the same views I did in 1962, except that I no longer view anhedonia (which I now prefer to call hypohedonia) as playing so crucial a role as I did under the influence of my analytic supervisor, Dr Glueck. A basic feature of my theory about molar aberrations in the interpersonal domain combines two notions. First, the impairment of learned functions attributable to the higher-level consequences of the integrative defect depends on how mixed (variable, unpredictable) the stochastic reinforcement schedule is; second, there is an asymmetry in the effect of an exaggerated feedback from positive and negative reinforcement centers to the perceptual-cognitive centers of the brain. This is admittedly rather vague, and involves postulating a black box model of functional relations that must be going on "in there" to explain the normal case. On reasoning similar to what I offered in 1962, the idea is that linkages between plus and minus limbic system centers and perceptual-cognitive brain subsystems grow in accordance with a decelerated mathematical function, perhaps even with an ogival function, although this is not crucial but makes the argument stronger. When we have a stochastic schedule, as, for instance, the care-giver being variable, with certain nurturant inputs activating positive Olds centers and a frowning face or rough handling activating negative Olds centers, the reasoning is that the positive and negative are in competition in stimulating and suppressing the perceptual-cognitive process. Over a period of time, in a highly variable and mixed (positive/ negative) social regime, the exaggeration of the feedback in the decelerated region of the curve will be less than the exaggeration in the linear or positively accelerated region. As a result of this parametric difference, a sequence of social learnings in which the appetitive predominates will be somewhat retarded by the aversive feedback, whereas a sequence of occasions predominantly aversive will be somewhat souped up by the exaggerated positive feedback in the less decelerated (or positively accelerated) region. The result of this quantitative asymmetry over the long haul in a given behavior domain will be what I called *aversive drift,* so that in addition to plus and minus associations being somewhat more "scrambled" in the schizotaxic brain, they will also tend to shift in the aversive direction. In such a theory, Rado's pain-dependent pleasure (or Freud's moral masochism), Rado's anhedonia, and Bleuler's ambivalence are all subsumed under the qualitative heading of ambivalence. Hypohedonia (too much dampening of pleasure at the high end of the hedonic continuum) and pain dependency or moral masochism (getting too much strengthening at the low end) and ambivalence in the middle region are all simple manifestations of the mixing of emotive signals. That is, they are all simply *ambivalence as manifested at different locations on the hedonic continuum.*

One does not attempt to derive all of the social malcommunication directly from the schizotaxic "cognitive slippage." The process of social learning leads to impaired consensual validation and to aberrations in verbal and gestural communication of the sort emphasized by psychodynamic and family theorists. But what gets this social process rolling initially is the combination of affective scrambling, aversive drift, and cognitive slippage as parametric features of the molar acquisition functions, and these arise from the schizotaxic defect.

In Rado's terminology, the schizotype is not a different category from the schizophrene. The schizophrene is a schizotype who is decompensated, either within the pseudoneurotic range, or *disintegrated* (that is, psychotic), and then, in the late chronic stages if he gets there, what Rado calls the *deteriorated* schizotype. The relationship of schizophrenia to schizotypy is represented by the word *compensation* by analogy to the extent to which the patient with kidney disease or cardiac disease is clinically compensated. As we think of symptomatic neuroses as always built on character neurosis in psychoanalysis, similarly we think of schizophrenia, whether of the psychotic or pseudoneurotic ("borderline") variety, as built on the schizotypal personality structure. And the schizotypal personality structure has evolved by social learning processes when the schizotaxic CNS is subjected to the kind of stochastic schedule (variable *and* double sign) of rewards and punishment that care-givers, peers, and life generally provide all of us.

I conjecture that hypokrisia is an endophenotype (inner state in the causal chain between the DNA and the exophenotype, the overt behavioral dispositions) for which a dominant schizogene is completely penetrant. I am aware that the major locus idea is an

unpopular one among behavior geneticists and that some, such as my friend and former colleague Irving I. Gottesman, PhD, consider it to have been refuted.[44-48] This is not the place to go into details of that, and I am not competent as a behavior geneticist. I content myself with saying that the alleged refutations do not deal with the type of complicated causal model that I postulate. In designing empirical tests of a theory, one must be sure to "give the theory its head" without being circular, sometimes a thorny problem. I am skeptical as to how adequately we can test a major locus theory with polygenic potentiators by employing formal diagnosis analyzed by conventional methods. Consider the following factors, an incomplete list that surely underestimates the true causal complexity: in studying families, we must either exclude with near certainty, or somehow "correct for," genophenocopies like the SHAITU syndrome described below, meanwhile keeping in mind that *its* components operate as polygenic and environmental potentiators for true schizophrenia. The analysis must take account of the sex difference in impact of schizotypy on fertility, and these numerical values cannot be safely extrapolated from the data on full-blown schizophrenia. There may be positive or negative assortative mating for the schizogene taken over the whole range of clinical compensation, despite its negligible amount for formal diagnosis. There will almost certainly be assortative mating for the polygenic potentiators, and some of these correlations could be negative (eg, dominance). The potentiators are not likely to have equal impact on fertility for the sexes, partly on their own, but partly because of different potentiating effects for decompensation and, hence, fertility. The parental "side-concentration" of polygenes must be included in one's statistics, because a proband (who has decompensated or else would not have been ascertained) is more likely to have received his or her potentiating polygenes from both sides than from the schizotypal parent, since if the latter carried a heavy loading of them, he or she would have been less likely to mate. This side-concentration effect is also probably different for the sexes. Psychodynamically, one would expect differences in the potentiating effect of identification with the schizotypal parent depending on whether that parent is the same sex as the proband, and this complication will interact with the sex difference in fertility. Finally, we only locate families in which some member has decompensated, and the diagnostic statistics suggest that there must be around 10 times as many schizotypes in the population as there are diagnosed schizophrenes. The family statistics for this path diagram, even if the small and unstable figures for second-degree relatives are included, will involve fewer equations than unknowns, so no good test is available.

I am not troubled by the argument that "this all makes things too complicated to test," since I think that is the real situation when the measured variable is formal diagnosis. The diagram of conjectured causal influences in my theory is oversimplified from what complexity we must assume to be the case, and it is salutary to compare it with a similar diagram for diabetes[45(p214)] or a typical diagram of the pathophysiology of kidney disease and its effects on blood pressure, cardiac function, etc. One should take it for granted that the brain is at least as complicated as the kidney. This is why I favor emphasis on indicators closer to the gene such as psychophysiologic and soft neurologic measures, and perhaps psychometrics, although here I have become more skeptical. We also need good indicators of subtle cognitive slippage, but, with the possible exception of attention deficit, these have so far been rather disappointing.[49-53] The occurrence of a strongly taxonic statistical structure manifested by schizotaxic indicators among parents is a neglected approach. The Bayes' Theorem curve of inverse probabilities of taxon membership from a set of quite fallible dichotomous signs is U-shaped for a taxonic situation, as is the distribution for a single quantitative indicator when sufficiently valid.[33,54,55] A striking example of this is the distribution of P50 scores for the first-degree relatives found by Freedman's group,[28] especially since the incidence of sign-positives is about 50%, as the dominant gene theory predicts. Replication of this finding is of first-rate importance. While it is mathematically possible (by suitable ad hoc adjustments) to square this kind of curve with a polygenic model, that is of course weaker than a successful prediction of it, and would be hard to interpret physically. The polygenic theorist has to conjecture that people have a high negative assortative mating for this neurophysiology trait, or for a highly valid behavioral proxy of it; and that the threshold "just happens" to be at the 50% cut predicted by the dominant gene theory. If even a few psychophysiologic indicators behaved this way, the polygenic theory would appear badly ad hoc'd. Similarly, if a set of high valid schizotaxic indicators failed to reveal a taxonic statistical structure, a major locus theory would be strongly discorroborated, or, I should say, definitely refuted.

In that connection I should say something about why I adopt an altered semantics from that generally received in genetics. In my theory there is a set of heritable traits, presumably polygenic in origin, around a dozen in number, that are *potentiators* of schizophrenia, that raise the probability of clinically diagnosable illness in a schizotype who has a heavy loading of them (Figure). The reason I prefer the word *potentiator* to the geneticists' familiar word *modifier* is that the conception is different and therefore we need a different term. In genetics, a modifier gene (or system of polygenes), the extreme case being that of a single gene with dominant epistasis, "gets into the causal chain" between the DNA and some trait manifested in the exophenotype, for example, a gene that affects the amount of substrate that must be available for the main gene of interest to generate the causal chain that results in some exophenotypic property of the organism. That is not the kind of model involved in a theory such as mine. For example, social introversion is one of the variables that I conjecture to potentiate the probability of schizophrenic decompensation in a schizotype. The evidence is strong for the polygenic heritability of social introversion,[56-59] so this does not play an ad hoc role in the theory. The same is true for most of the other polygenic potentiators, such as dominance, anxiety, energy level, mesomorphy, sex drive, etc, all of which are known to be partly heritable in humans and other mammals. However, the causal model here is not like that of a modifying gene in the fruit fly "getting in the way" of another gene's expression in the phenotype. The schizotaxic gene produces the endophenotypic hypokrisia that gives rise to certain molar-level parametric aberrations in acquiring, retaining, and generalizing positive and negative social conditionings. However, I do not presume, and I do not know anybody favorable to my theory who presumes,

that there is a biochemical factor, produced by the polygenes determining variance of social introversion in the normal range, that interferes with or enhances the expression of the schizogene as a social learning parameter. Rather, we get two different dispositions in the exophenotype that interact with the social environment to move a schizotype in the direction of schizophrenic decompensation. That being a different situation from the traditional one, we need a different word than *modifier.* Another example would be intelligence, a strongly heritable disposition, which we do not conjecture to "modify" schizotaxic soft neurology or aversive drift, but which may very well alter probability of decompensation, as in the schizoid college professor who survives comfortably in our extroverted, competitive society because academia may provide a special niche for deviant persons with high IQ.

I take expressivity to be the primary concept, although genetics books generally introduce penetrance first (ie, *"when* penetrant, a gene may vary in expression"). It seems to me that expressivity is the basic concept both conceptually and mathematically. For any given quantitative indicator of a gene, unless there is zero overlap of the expressivity distribution functions (in which case we have 100% penetrance), the penetrance coefficient is conventional, being a question of where the scientist locates the cutting score; whereas the expressivity function is an objective fact of nature, although it may at times be difficult for us to ascertain it. So, while one may accept "clinical penetrance" as a marginally satisfactory item for the proportion of schizotypes who develop a diagnosable schizophrenia, I do not find it a precise notion. Another reason is that, contrary to the usual geneticists' use of language, schizophrenia is not a "trait" but is a collection of imperfectly correlated traits. Even if there were no arbitrariness in the cutting score on expressivity per *trait,* there would still be an arbitrariness involved in how many traits must pass their respective cutting scores before a person is considered to have the "trait" called schizophrenia. I do not think of these refinements as hair-splitting semantics, but as important conceptual distinctions without which one cannot think clearly about the genetics of something as complicated as schizophrenia.

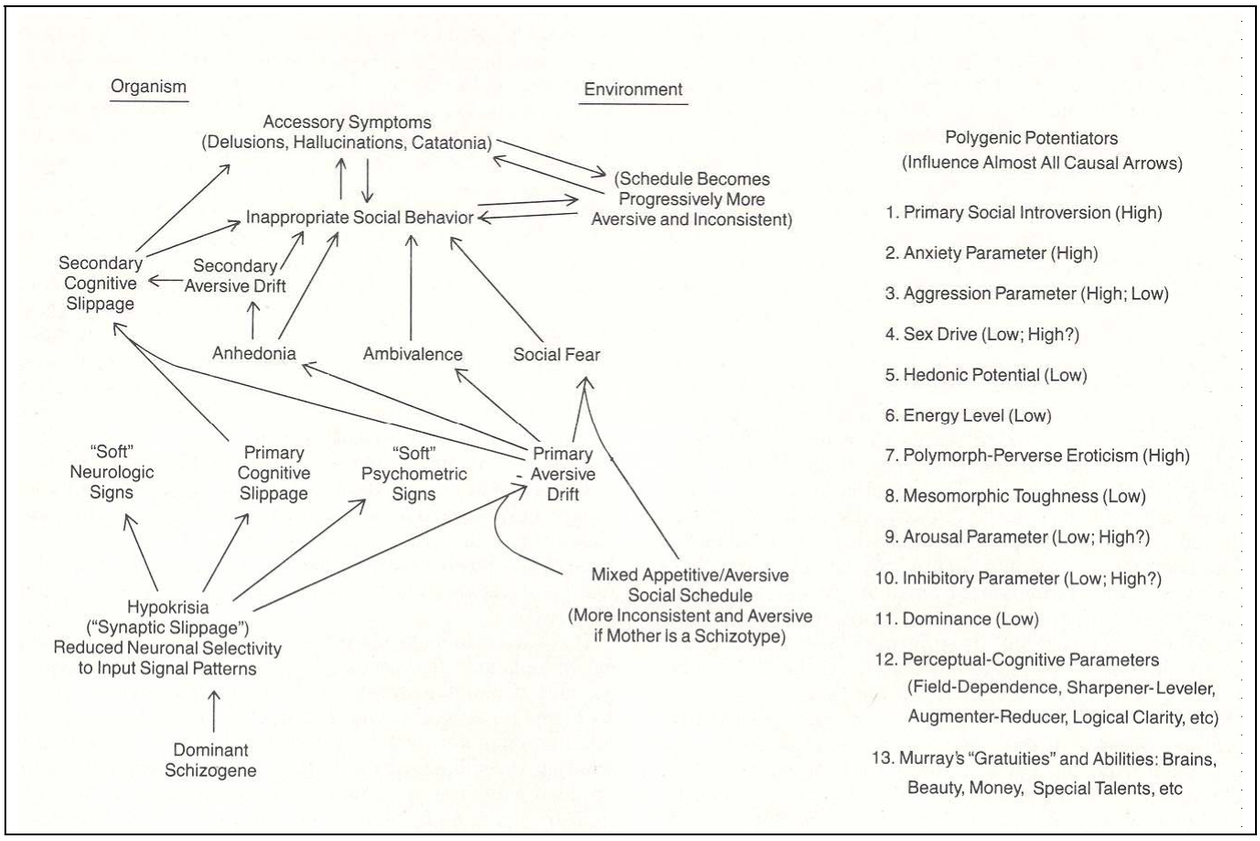
Whether there are any true phenocopies of schizophrenia I do not know, but I am strongly inclined to doubt it. One might use the term *genocopy* to refer to certain combinations of polygenes that can give rise to a syndrome quite similar to schizotypy. I doubt their existence, because while plausible candidates exist in the cognitive and, even more, the interpersonal-social domain, I doubt that there are any polygenic systems determining these that could also give rise to a taxon exhibiting the soft neurology and psychophysiology of the schizotaxic brain. One may ask, what could such polygenic systems be? There is a reasonable chance for a syndrome that might (with present methods) be difficult to distinguish from the schizotype in some degree of compensation, *if we did not have the soft neurology and psychophysiology to look at.* Consider a person without the schizogene who is low on dominance (I will call that "submissive"), hypohedonic, anxietous, and introverted, three of which are known to be strongly heritable and presumably polygenic, and I conjecture hypohedonia to be also, although evidence here is sketchy as yet.[56-62] To these unfortunate genetic loadings we now add one or more traumas in the developmental period, which could either be physical (birth injury or viral infection) or social (maternal rejection or incestuous rape). Finally, on that bad genetic and bad social learning history, we superimpose a run of bad luck in adult life. Like Sir Karl Popper, I attach great importance to "luck" and look on it as one of the most undervalued concepts in social science.[30(pp220,221),63,64(PP402-407),65] I call this conjectural syndrome "SHAITU," an acronym formed from the initial letters of the words *submissive, hypohedonic, anxietous, introverted, traumatized,* and *unlucky.* Perhaps an *R* should be added for *rageful,* but I currently incline to think rage is not a polygenic primary but derivative from the others, especially from the anxiety and hypohedonia. Hypohedonia results in inadequate "softening" of the emergency affects fear and rage.[2-4,60-62] It might be hard for the most skilled clinician to discriminate such an adult from the schizotype, although I believe that the peculiar schizoid thought disorder shown in some kinds of subtle syntax and semantics would not be present. My prediction is that if the SHAITU syndrome does exist as a clinical entity, it will be discriminable by absence of the soft neurology and psychophysiology of the schizotaxic brain.

Unlike some of my "dustbowl empiricist" colleagues at the University of Minnesota, I am willing to rely on general theoretical considerations to fill out such a picture, as long as hard quantitative data are not adverse. For example, it seems foolish to ignore general psychological theory about identification, role modeling, and the like. I am therefore pretty confident that while no such thing as the specific etiology of the schizophrenogenic mother exists (absent the schizogene as a necessary condition), when we get good studies using sensitive instruments, it will be found that the child-rearing practices and attitudes of mother are potentiators of subsequent schizophrenia. I also predict that there will be a greater impact of mother's personality than of father's in this respect. But I say this on the basis of clinical impressions and general psychological theory, realizing that the present evidence, based almost wholly on the statistics of formal diagnosis, does not support any appreciable distinction between the impact of the two parents.

CONJECTURES AND RESEARCH STRATEGIES

Emboldened by my earlier success as a minor prophet, based as it was on scanty evidence at the time, I conclude by recording some "risky predictions," in harmony with my neo-Popperian philosophy of science.[65-70] These risky predictions follow from my theory and do not, I think, follow from others I know about. I am preparing a longer list for publication in another place, so these are offered merely as samples of falsifiable consequences, which, pending more extended development in the other paper, may suggest empirical studies to those interested in critically examining my theory. Unfortunately, some of the most interesting predictions involve measuring instruments not presently available, but that is not a departure from Popperian thinking. One reasons that" *When* we possess good measures of constructs C_{lf} C_2, … C_m, such and such correlation patterns will be found."

In the realm of soft neurology and psychophysiology, I conjecture that the smooth-pursuit eye movement[71] and P50 indicators are quasipathognomonic, functioning nearly perfectly as both exclusion and inclusion tests. In the language of the epidemiologist, they will have nearly perfect sensitivity and



Causal chains in schizophrenia, minimum complexity (from Meehl[40[pp16,190]]).

specificity, provided drug artifacts and coarse brain syndrome are carefully excluded. I conjecture that a quantified dysdiadochokinesia will also be pathognomonic when cerebellar lesion cases are excluded. (In the aforementioned article in preparation, I describe in some detail how I think such a test should be instrumented and numerified.) I have somewhat more doubt about a vestibular indicator, although I think it has a chance to have high validity when properly done.[72] On the dominant gene model of schizotaxia, the predicttion is that since the family data indicate that only about 10% of schizotaxic persons ever develop schizophrenia (and hence the base rate of schizotaxia must be in the neighborhood of 10%), then if we set a cutting score on a quasi-infallible neurologic or psychophysiologic indicator that will identify approximately 100% of schizophrenes or, relying on taxometric bootstrapsing, will identify 100% of schizotypes whether decompensated or not; then such an indicator, when thus cut to yield a dichoto-mous sign, should yield 10% *apparent false-positives* in the general population. Formal diagnosis, or degree of decompensation, are here irrelevant, their only role being in bootstrapsing the strong indicator in the context of discovery.[33]

One crucial step in such bootstrapsing will be to show that 100% of the monozygotic twins of schizophrenes have the sign, and that among them its quantitative amount does not depend on clinical status. It is crucial in this kind of theorizing and its associated testing method that what we are trying to track is a CNS anomaly, not clinical disease, even of a borderline character. While the "schizophrenic spectrum" is not an objectionable notion, and is analogous to the varied clinical pictures presented by nonpsychiatric diseases, the concept can hamper one's genetic thinking if taken to require manifest psychopathology of all schizotypes. The geneticist expects to find elevated uric acid titer in the monozygotic twins of patients with gout, although only 5% of men with that biochemical endophenotype are clinically "gouty." We do not expect these "discordant" twins to manifest a small but detectable inflammatory tetrad (rubor, calor, dolor, and turgor) in the big toe, to be in the "gout spectrum" by suffering a "teeny bit of gout," so to speak. The genetics are elucidated via the endophenotype, not by a touch of inflammation in the toe.

I have less confidence in social, cognitive, and "personality" indicators, because of their relative remoteness in the long causal chain from the DNA to those kinds of learned molar level patterns. My *Manual for Use With Checklist of Schizotypic Signs*[73] was developed on a sample of patients with Hoch-Polatin syndrome seen by me in psychotherapy over the preceding decade. I had intended to carry out taxometric analysis on it by enlarging the sample with protocols from several colleagues, but it turned out that these local practitioners did not find the checklist items reliably ratable. Meanwhile, the *DSM-III* schizotypal criteria had preempted the field, although my checklist was used in the training of residents at several facilities around the country. I am still inclined to think it was a nice list, but proper taxometric analysis would require a larger sample than I have at my disposal.

I expect, as pointed out in my 1962 paper, that the typical genetic family configuration is that the schizophrene receives the dominant schizogene from one parent and most of the potentiating polygenes from the other, because if the schizotypal parent had a sizable loading of the polygenic potentiators, he or she would be less likely to have mated and have offspring. Despite the absence of known difference between mothers and fathers when diagnosable schizophrenia is the criterion, I still anticipate that more sensitive measures will support the conjecture that the schizotypal female married to a neurotic male (neuroticism being partly determinative of his object choice?) is more likely than matings going in the other direction.

This is also because I believe, on purely theoretical grounds, that having a schizotypal mother should be a slightly more unfavorable environmental factor than having a schizotypal father. Ignoring formal diagnosis in favor of bootstrapsed taxon membership, one would expect that the nonschizotaxic parent should show heightened average values of the polygenic variables when measures of them are available sufficiently free of the influence of schizotypy itself. This is because the potentiators social introversion, anxiety proneness, low hedonic capacity, low dominance, and so on should tend to be received more often by the schizophrenic proband from the nonschizoid parent.

We require 50% of the parents of schizophrenes to be in the taxon. We further require that there must be at least one schizotaxic parent per pair, although a small incidence of two schizotaxic parents can be expected, so we do not expect the value to be precisely 0.50 as a taxon rate. If a fallible dichotomous sign is tallied in a fourfold table, defined not by two *variables* but by the two *parents,* and the covariance $p_{ij} - p_i p_j$ (numerator of the phi coefficient) is calculated on that table, its value should be approximately one fourth the squared difference between the valid-positive and false-positive rates. With a quantitative indicator, the covariance should be one fourth the square of the difference between the taxon and complement means.[74] On the dominant gene theory, one expects family trees in which schizophrenia appears in three generations to be one-sided. This is not easily tested via recorded diagnosis of schizophrenia, because of the low clinical penetrance; but using high probabilities of taxon membership obtainable by a combination of schizotaxic signs, this lateral familial concentration should be easier to detect. A "normal" parent with positive smooth-pursuit eye movement should also be positive on P50 and conversely, and I predict this to be independent of clinical status. Psychophysiologic and soft neurology indicators that are not pathognomonic of the taxon should show numerical separations (mean differences of overlaps) that follow the taxon apart from diagnosed schizophrenia, and apart from the measures of the polygenic potentiators.

It is harder to make strong predictions about the biochemical endophenotype, because doing it right would require single-unit stimulation research of a kind we cannot readily do with human subjects. One thinks, for instance, of repeated stimulation of a neuron by varied input patterns to ascertain whether the spike probability is (1) enhanced and (2) dedifferentiated when the preparation is perfused with extracellular fluid from a nonschizophrenic schizotaxic's brain. One might hope to detect this by using some other experimentally available primate, since the neurotransmitters are very much the same for us and our primate relatives (for that matter, between us and the white rat). The trouble with that experimental idea is its assumption that the schizogene is a mutation from the "normal type," wherein some substance is aberrated and hence defective in stabilizing the cell membrane, yielding hypokrisia. This is not a solid consequence because we have to rely further on the auxiliary theory that the aberrated substance occupies the sites. Further, it may be that what we consider the normal gene here is a mutation in the evolution of humans, and that the former "wild type" lacks it. This possibility I have never seen mentioned in discussions of why a conjectural schizogene has not been eliminated by now. If one operates within a framework of primate evolution, this would seem to be a live option. The "normal" gene would be a mutation in primate evolution that has a selective advantage, has been slowly taking over, and has now reached a .95 gene frequency (for a. 10 schizotaxic base rate, dominant model).

Finally, I offer the rash prediction that a sizable minority of patients not diagnosed schizophrenic, major affective disorder, or an organic brain condition (the miscellany of neuroses and personality disorders that make up the rest of "functional" psychopathology) are schizotypes. My subjective estimate is that this proportion will be in the neighborhood of 35%, based on Checklist and MMPI patterns found in my private therapy practice, plus taxometric results in the University of Minnesota Hospital MMPI records.[31,33] As examples, I anticipate that most of the patients called borderline[75] are schizotypes; that at least half of the patients with what is called Briquet's syndrome are schizotypes; that many persons with a chronic (nonepisodic) low-level "depression," not meeting present criteria for major affective disorder, are schizotypes; and that many patients who in the old nomenclature were said to have anxiety state are schizotypes. Like Bleuler, I expect the majority of patients who in the old days would have been called hypochondriacs, and many patients with multifarious fluctuating psychosomatic disorders, are schizotypes. Following Bleuler (and my colleague Heston[76,77]) I expect, if not the majority, at least a very large minority of what used to be called constitutional psychopathic inferiors, then psychopaths, and now sociopaths, are schizotaxic. The current categorization of the latter is (in my view wrongly) focused on *social impact* criteria of psychopathy rather than the purely "psychological" traits emphasized by Cleckley[78] and Lykken,[79] and reflected in the MMPI psychopathic deviate pattern.[80,81]

These are risky predictions and out of line with what most practitioners and behavior geneticists now believe. However, having been a successful prophet when going strongly against the received doctrines a quarter of a century ago, I do not mind going out on a limb again.

SUMMARY

The core conjecture is that a dominant autosomal schizogene, completely penetrant for an endophenotypic parametric aberration in the neuron's synaptic signal selectivity (hypokrisia), produces a unique kind of CNS integrative defect (schizotaxia), characterized functionally by its influencing multiple psychophysiologic and soft neurologic indicators and by parametric aberrations in the acquisition and activation functions of diverse molar psychisms (perceptual-cognitive, semantic, motivational, and affective). These aberrations are considered to flow from the primary "synaptic slippage," although not equally closely or in the same way; in that sense they all stem from Bleuler's core defect, "associative loosening." The imposition of mixed social reinforcement schedules on these dispositions results in a schizotypal personality structure. Core features of this personality include interpersonal alienation, ambivalence, dereism, autism, cognitive slippage, and aversive drift. The great majority of schizotypes remain free of diagnosable mental disorder, but a minority (around 10%) develop schizophrenia. These rare persons are at higher risk because of potentiating polygenes for

other, independent dimensions (eg, anxiety proneness, introversion, and hypohedonia), as well as adverse developmental factors and adult stressors. In researching such a theory, certain methodologic guidelines (not "rules"!) should be kept in mind:

1. Indicators closer in the causal chain to the DNA are usually preferable; so, for example, research on soft neurology should pay off more than psychometrics, and the latter more than "spectrum" psychiatric symptoms or social impact.

2. The spectrum concept, while intrinsically valid, is not very useful in testing a theory of this sort.

3. Taxometric statistics are the preferred mode of analysis when testing a major locus conjecture, corresponding to a molar type (rather than dimension).

4. While a clear "marker" (two-way pathognomonic, with sensitivity = specificity = 1) of the schizogene would be handy, with suitable taxometric methods that ideal case is not necessary. However, if such a perfect marker were to exist, it could be detected by the taxometric Super-Bootstraps Theorem applied to fallible signs.

5. One should avoid employing indicators that are qualitatively similar because they are likely to show sizable factorial covariation that is taxometrically undesirable. (Conventional thinking about this is opposite to what is optimal in indicator properties.)

6. "Exact" statistics are less useful than multiple-indicator coherence; and point values, even if crudely examined, are preferable to mere significance tests.

7. One reason for working with a major gene conjecture until clearly falsified is its higher falsifiability, predicting values that a polygenic theory can often be fitted to but usually will not have predicted.

8. Taxometric bootstrapsing usually leads to taxometric drift and hence conceptual drift. This is desirable so long as provision is made in a research program to return to the schizophrenia construct at later stages. For example, a taxometrically bootstrapsed schizotaxic sign having little or no similarity to anything in the clinical schizophrenia syndrome can be studied in schizophrenic pedigrees.

9. Different levels (molar and molecular) of explanation remain appropriate for different classes of indicators, despite theoretical conjectures as to interlevel derivability.

10. Hence, what we know about schizophrenia psychodynamically and psychometrically is easily compatible with a scientific etiology that is neurologic and genetic. What are inherited are merely aberrant (quantitative) dispositions to acquire socially learned contents (motives, cathexes, defense mechanisms, unconscious fantasies, etc).

11. At this stage, a theory should explain the big trends, not everything. However, smaller trends may be important as leads if they are theoretically interesting, such as the nailfold anomaly, or even (as one clinician of my acquaintance alleged) a tendency to malocclusion slightly higher than in the general population.

12. Statistical models for testing the theory on family patterns must not oversimplify to such an extent that nuisance correlations predicted by the theory itself (eg, assortative mating for polygenic potentiators and differential impact on fertility) are treated as negligible.

13. Genetic semantics needs some cleaning up when applied to the behavioral domain ("modifier," "heterogeneity," "penetrance," "expressivity," "trait," and "phenotype").

14. When there is a tradeoff between mathematical elegance (precision, optimality, and maximum likelihood estimators) and epistemic strength, the latter should be preferred.

15. We should keep in mind, whether theorizing or experimenting, that the brain is at least as complicated as the kidney.

References

1. Meehl PE. Schizotaxia, schizotypy, schizophrenia. *Am Psychol.* 1962;17:827-838. Reprinted in: Meehl PE. *Psychodiagnosis: Selected Papers.* Minneapolis: University of Minnesota; 1973:135-155.
2. Rado S. *Psychoanalysis of Behavior.* New York, NY: Grune & Stratton; 1956.
3. Rado S. Theory and therapy: the theory of schizotypal organization and its application to the treatment of decompensated schizotypal behavior. In: Scher SC, Davis HR, eds. *The Out-Patient Treatment of Schizophrenia.* New York, NY: Grune & Stratton; 1960.
4. Rado S, Daniels G. *Changing Concepts of Psychoanalytic Medicine.* New York, NY: Grune & Stratton; 1956.
5. Gunderson J, Siever L, Spaulding E. The search for a schizotype: crossing the border again. *Arch Gen Psychiatry.* 1983;40:15-22.
6. Kraepelin E; Robertson GM, ed; Barclay RM, trans. *Dementia Praecox and Paraphrenia.* Huntington, NY: Krieger; 1971 (original work published 1909-1913; original translation of selected portions published 1919).
7. Bleuler E; Zinkin J, trans. *Dementia Praecox.* New York, NY: International Universities Press; 1950 (original work published 1911).
8. Bleuler E; Brill AA, trans-ed. *Textbook of Psychiatry.* New York, NY: Macmillan Publishing Co Inc; 1924.
9. Fish B. The study of motor development in infancy and its relationship to psychological functioning. *Am J Psychiatry.* 1961; 117:1113-1118.
10. Fish B. Biologic antecedents of psychosis in children. In: Freedman DX, ed. *Biology of the Major Psychoses, Research Publications—Association for Research in Nervous and Mental Disease.* New York, NY: Raven Press; 1975;54:49-83.
11. Fish B. Neurobiologic antecedents of schizophrenia in children. *Arch Gen Psychiatry.* 1977;34:1297-1313.
12. Fish B. Characteristics and sequelae of the neurointegrative disorder in infants at risk for schizophrenia: 1952-1982. In: Watt NF, Anthony EJ, Wynne, LC, Rolf JE, eds. *Children at Risk for Schizophrenia: A Longitudinal Perspective.* New York, NY: Cambridge University Press; 1984:423-439.
13. Dollard J, Miller NE. *Personality and Psychotherapy.* New York, NY: McGraw-Hill International Book Co; 1950.
14. Rosanoff AF, Handy LM, Plesset IR, Brush S. The etiology of so-called schizophrenic psychoses with special reference to their occurrence in twins. *Am J Psychiatry.* 1934;91:247-286.
15. Angyal A, Blackman N. Vestibular reactivity in schizophrenia. *Arch Neurol Psychiatry.* 1940;44:611-620.
16. Angyal A, Blackman N. Paradoxical vestibular reactions in schizophrenia under the influence of alcohol, of hyperpnea and $C0_2$ inhalation. *Am J Psychiatry.* 1941;97:839-903.
17. Angyal A, Sherman N. Postural reactions to vestibular stimulation in schizophrenic and normal subjects. *Am J Psychiatry.* 1942;98:857-862.
18. Freeman H, Rodnick EH. Effect of rotation on postural steadiness in normal and in schizophrenic subjects. *Arch Neurol Psychiatry.* 1942;48:47-53.
19. Hoskins RG. *The Biology of Schizophrenia.* New York, NY: WW Norton; 1946.
20. Lewis NDC. Constitutional factors in dementia praecox. *Nerv Ment Dis Monogr.* 1923: No. 35.
21. Sheldon W, Lewis NDC, Tenney AM. Psychotic patterns and physical constitution: A thirty year follow-up of 3800 psychiatric patients in New York State. In: Sankar D V Siva, ed. *Schizophrenia: Current Concepts and Research.* Hicksville, NY: PJD Publications; 1969.
22. Kallmann FJ. The genetic theory of schizophrenia: an analysis of 691 schizophrenic twin index families. *Am J Psychiatry.* 1946;103:309-322.
23. Heinrichs DW, Buchanan RW. Significance and meaning of neurological signs in schizophrenia. *Am J Psychiatry.* 1988;145: 11-18.
24. Hoch PH, Polatin P. Pseudoneurotic forms of schizophrenia. *Psychiatr Q.* 1949;3:248-276.
25. Hoch PH, Cattell JP, Strahl MO, Pennes HH. The course and outcome of pseudoneurotic schizophrenia. *Am J Psychiatry.* 1962; 119:106-115.

26. Manschreck TC, Maher BA, Rucklos ME, Vereen DR. Disturbed voluntary motor activity in schizophrenic disorder. *Psychol Med.* 1982;12:73-84.
27. Meehl PE. Schizotaxia as an open concept. In: Rabin AI, Zucker R, eds. *Studying Persons and Lives.* New York, NY: Springer Publishing Co Inc; ~~in press.~~ 1990:248-303.
28. Freedman R, Adler LE, Baker N, Waldo M, Mizner G. Candidate for inherited neurobiological dysfunction in schizophrenia. *Somatic Cell Mol Genet.* 1987;13:479-484.
29. Meehl PE. Theory and practice: Reflections of an academic clinician. In: Bourg EF, Bent RJ, Callan JE, Jones NF, McHolland J, Strieker G, eds. *Standards and Evaluation in the Education and Training of Professional Psychologists: Knowledge, Attitudes, and Skills.* Norman, Okla: Transcript Press; 1987:7-23.
30. Meehl PE. MAXCOV-HITMAX: a taxonomic search method for loose genetic syndromes. In: Meehl PE. *Psychodiagnosis: Selected Papers.* Minneapolis: University of Minnesota; 1973:200-224.
31. Golden R, Meehl PE. Detection of the schizoid taxon with MMPI indicators. *J Abnorm Psychol.* 1979;88:217-233.
32. Golden R, Meehl PE. Detection of biological sex: an empirical test of cluster methods. *Multivar Behav Res.* 1980; 15:475-496.
33. Meehl PE, Golden R. Taxometric methods. In: Kendall P, Butcher J, eds. *Handbook of Research Methods in Clinical Psychology.* New York, NY: John Wiley & Sons Inc; 1982:127-181.
34. Medicine. *Encyclopaedia Britannica.* Edinburgh, Scotland: A Bell and C Macfarquhar; 1771;3:58-169.
35. Meehl PE. Diagnostic taxa as open concepts: metatheoretical and statistical questions about reliability and construct validity in the grand strategy of nosological revision. In: Millon T, Klerman GL, eds. *Contemporary Directions inPsychopathology.* New York, NY: Guilford; 1986:215-231.
36. Cronbach LJ, Meehl PE. Construct validity in psychological tests. *Psychol Bull.* 1955;52:281-302. Reprinted in: Meehl PE. *Psychodiagnosis: Selected Papers.* Minneapolis: University of Minnesota; 1973:3-31.
37. Pap A. Reduction-sentences and open concepts. *Methodos.* 1953;5:3-30.
38. Pap A. *Semantics and Necessary Truth.* New Haven, Conn: Yale University Press; 1958.
39. Pap A. *An Introduction to the Philosophy of Science.* New York, NY: The Free Press; 1962.
40. Meehl PE. Specific genetic etiology, psychodynamics and therapeutic nihilism. *Int J Ment Health.* 1972;1:10-27. Reprinted in: Meehl PE. *Psychodiagnosis: Selected Papers.* Minneapolis: University of Minnesota; 1973:182-199.
41. Meehl PE. Specific etiology and other forms of strong influence: some quantitative meanings. *J MedPhilos.* 1977;2:33-53.
42. Hebb DO. *The Organization of Behavior: A Neuropsychological Theory.* New York, NY: John Wiley & Sons Inc; 1949.
43. McGhie A, Chapman J. Disorders of attention and perception in early schizophrenia. *Br J Med Psychol.* 1961;34:103-117. Reprinted in: Buss AH, Buss EH, eds. *Theories of Schizophrenia.* New York, NY: Atherton Press; 1969:47-75.
44. Gottesman II, Shields J. *Schizophrenia and Genetics: A Twin Study Vantage Point.* Orlando, Fla: Academic Press Inc; 1972.
45. Gottesman II, Shields J. *Schizophrenia, The Epigenetic Puzzle.* New York, NY: Cambridge University Press; 1982.
46. O'Rourke DH, Gottesman II, Suerez BK, Rice J, Reich P. Refutation of the general single locus model for the etiology of schizophrenia. *Am J HumGenet.* 1982;34:630-649.
47. McGue M, Gottesman II, Rao DC. The transmission of schizophrenia under a multifactorial threshold model. *Am J Hum Genet.* 1983;35:1161-1178.
48. Holzman PS, Kringlen E, Matthysse S, Flanagan SD, Lipton RB, Cramer G, Levin S, Lange K, Levy DL. A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of discordant twins. *Arch Gen Psychiatry.* 1988;45: 641-647.
49. Berenbaum H, Gottesman II, Oltmanns TF. Formal thought disorder in schizophrenics and their twins. *J Abnorm Psychol.* 1985;94:3-16.
50. Kagan DL, Oltmanns TF. Matched tasks for measuring single-word, referent communication: the performance of patients with schizophrenic and affective disorders. *J Abnorm Psychol.* 1981;90:204-212.
51. Neale JM, Oltmanns TF, Harvey PD. The need to relate cognitive deficits to specific behavioral referents of schizophrenia. *Schizophr Bull.* 1985;11:286-290.
52. Knight RA. Converging models of cognitive deficit in schizophrenia. In: Spaulding WD, Cole JK, eds. *Theories of Schizophrenia and Psychosis: Nebraska Symposium on Motivation 1983.* Lincoln: University of Nebraska Press; 1984;31:93-156.
53. Nuechterlein KH, Dawson ME. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophr Bull.* 1984;10:160-203.
54. Golden R, Tyan S, Meehl PE. *Detecting latent clinical taxa, VII: Maximun likelihood solution and empirical and artificial data trials of the multi-indicator multi-taxonomic class normal theory* (report No. PR-74-5). Minneapolis: University of Minnesota, Research Laboratories of the Department of Psychiatry; 1974.
55. Golden R, Meehl PE. *Detecting latent clinical taxa, VIII: A preliminary study in the detection of the schizoid taxon using MMPI items as indicators* (report No. PR-74-6). Minneapolis: University of Minnesota, Research Laboratories of the Department of Psychiatry; 1974.
56. Fuller JL, Thompson WR. *Foundations of Behavior Genetics.* St Louis, Mo: CV Mosby Co; 1978.
57. Manosevitz M, Lindzey G, Thiessen DD. *Behavioral Genetics: Methods and Research.* East Norwalk, Conn: Appleton & Lange; 1969.
58. Plomin R. *Development, Genetics and Psychology.* Hillsdale, NJ: Lawrence Erlbaum Associates; 1986.
59. Tellegen A, Lykken DT, Bouchard TJ, Wilcox K, Segal N, Rich S. Personality similarity in twins reared apart and together. *J Pers Soc Psychol.* 1987;54:1031-1039.
60. Meehl PE. Genes and the unchangeable core. *VOICES.* 1974/ 1975;10:25-35.
61. Meehl PE. Hedonic capacity: some conjectures. *Bull Menninger Clin.* 1974;39:295-307.
62. Meehl PE. 'Hedonic capacity' ten years later: Some clarifications. In: Clark DC, Fawcett J, eds. *Anhedonia and Affective Deficit States.* New York, NY: PMA; 1987:47-50.
63. Meehl PE. Psychopathology and purpose. In: Hoch P, Zubin J, eds. *The Future of Psychiatry.* New York, NY: Grune & Stratton; 1962:61-69.
64. Meehl PE. A critical afterword. In: Gottesman II, Shields J. *Schizophrenia and Genetics: A Twin Study Vantage Point.* Orlando, Fla: Academic Press Inc; 1972:367-416.
65. Meehl PE. Theoretical risks and tabular asterisks: Sir Karl, Sir Ronald, and the slow progress of soft psychology. *J Consult Clin Psychol.* 1978;46:806-834.
66. O'Hear A. *Karl Popper.* Boston, Mass: Routledge & Kegan Paul; 1980.
67. Popper KR. *The Logic of Scientific Discovery.* New York, NY: Basic Books Inc Publishers; 1959 (original work published 1934).
68. Popper KR. *Conjectures and Refutations.* New York, NY: Basic Books Inc Publishers; 1962.
69. Popper KR. *Realism and the Aim of Science.* Totowa, NJ: Rowman and Littlefield; 1983;I.
70. Schilpp PA, ed. *The Philosophy of Karl Popper.* LaSalle, 111: Open Court; 1974.
71. Iacono WG. Eye movement abnormalities in schizophrenia and affective disorders. In: Johnston CW, Pirozzolo FJ, eds. *Neuropsychology of Eye Movements.* Hillsdale, NJ: Lawrence Erlbaum Associates; 1988:115-145.
72. Levy DL, Holzman PS, Proctor LR. Vestibular dysfunction and psychopathology. *Schizophr Bull.* 1983;9:383-438.
73. Meehl PE. *Manual for use with checklist of schizotypic signs* (report No. PR-73-5). Minneapolis: University of Minnesota, Research Laboratories of the Department of Psychiatry; 1964.
74. Golden R, Meehl PE. Testing a single dominant gene theory without an accepted criterion variable. *Ann Hum Genet.* 1978;41: 507-514.
75. Kroll J, Sines L, Martin K, Lari S, Pyle R, Zander J. Borderline personality disorder. *Arch Gen Psychiatry.* 1981;38:1021-1026.
76. Heston LL. Psychiatric disorders in foster home reared children of schizophrenic mothers. *Br J Psychiatry.* 1966;112:819-825.
77. Heston LL. The genetics of schizophrenia and schizoid disease. *Science.* 1970;167:249-256.
78. Cleckley HM. *The Mask of Sanity.* 5th ed. St Louis, Mo: CV Mosby Co; 1976.
79. Lykken DT. Psychopathic personality. In: Corsini RJ, ed. *Encyclopedia of Psychology.* New York, NY: John Wiley & Sons Inc; 1984;3:165-167.
80. Dahlstrom WG, Welsh GS, Dahlstrom LE. *An MMPI Handbook: Clinical Interpretation.* 2nd ed. Minneapolis: University of Minnesota; 1972;1.
81. Marks PA, Seeman W. *Actuarial Description of Abnormal Personality.* Baltimore, Md: Williams & Wilkins; 1963.