#109

Specific Etiology and Other Forms of Strong Influence: Some Quantitative Meanings

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In recent years several issues, some of great moral, legal, and policy importance, have arisen which impel the philosophically inclined to seek clarification about the meaning of "disease" and "disease entity." Examples are the controversy over whether "mental illness" is properly so called (see, e.g., Ausubel 1961; Szasz 1961) and the related questions of involuntary civil commitment (Livermore, Malmquist, and Meehl 1968) or the insanity defense to a criminal charge (Livermore and Meehl 1967; Goldstein 1967; see generally Brooks 1974; Miller et al. 1976). Resolution of current scholarly dispute concerning roles of genetic and social learning factors in the causation of schizophrenia (see Gottesman and Shields, in press, and references cited therein) appears to hinge only partly on getting further facts; it also hinges (in my view, increasingly) on methodological clarification of the relation between a taxonomic (typological, "entity"-like) concept and conjectured empirical causal explanations of it. Some clinicians in the behavior-modification tradition believe (quite wrongly) that their powerful technological approach is incompatible with psychiatric nosology and (even more wrongly) that explanation of behavior dispositions in disease-entity terms is somehow prescientific, tautologous, or circular. Revival of interest in criticizing Koch's etiological position and its historical alternatives (Penn and Dworkin 1976) and the related current emphasis upon the ecology, economics, and sociology of disease is another example. Reflection upon these matters (especially the confusions in genetic psychopathology) persuades me that the somewhat fuzzy notion of specific etiology is one cause of our contemporary puzzlement and that an effort to tease apart and formalize some of its components and varieties would be worthwhile. It goes without saying that I so not see such an endeavor as solving the list of problems above; I

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33

merely urge that preliminary clarification is probably a necessary element in their solution. The exercise is primarily philosophical in nature, and the formalism is employed solely for the purpose of explicating and rigorizing concepts—not, as should be apparent, with an eye to direct empirical application (as in, say, measurement of heritability). However, the unavoidable textual cumbersomeness will show, I trust, that I am not engaged in phony mathematical window dressing but endeavoring by means of the formalism, despite its abstract generality, to follow Charles Sanders Peirce's advice about "making our ideas clear."

Preliminary to setting out several formal meanings of "specific etiology" and related concepts, some general statements of a semiphilosophical sort may be in order. Space limitations prohibit a systematic defense of these points, which I shall therefore make succinctly and, in appearance but not by intent, perhaps rather dogmatically, referring the reader to other writings of mine on this and related topics (Meehl 1973, esp. chaps. 1, 5, 11–13).

In the development of a disease-entity concept from its earliest stages, the history of medicine reveals an "ideal type" which is approximated by the majority of disease entities, ultimately defined explicitly by their joint pathology and etiology. Initially a clinician calls attention to a syndrome, a cluster of signs and symptoms that he has observed in his practice—sometimes even a single patient may be exemplar and sole instance, although usually there would be more than that—including some account of the course and outcome, death or recovery with or without sequelae, and the like. Even in a fairly advanced state of knowledge concerning them, disease entities are at the clinical (symptom, complaint, course) level of analysis more or less loose clusterings, in the sense that complete statistical predictability from any symptom to any other symptom or set of symptoms does not obtain. Even the usually benign disorders may occasionally leave bad aftereffects or produce death; other diseases spoken of as "uniformly fatal" sometimes mysteriously recover. Prior to the elucidation of the specific etiology which, when identified, then becomes definitive of the disease entity and even permits our speaking of "latent" (subclinical, silent) disorders in the light of the pathologist's findings from biopsy or post mortem when the patient dies from some other cause, the disease entity is an open concept, in the sense of the late philosopher of science Arthur Pap (1953; 1962*a*, chap. 11; 1962*b*, chap. 3). I shall allow myself to expand somewhat on the notion of open concepts as they were introduced by Pap (and, more remotely and relied upon by him, by the logician and philosopher of science Rudolf Carnap, in his classic paper "Testability and Meaning" [1936, 1937]). We can identify three distinguishable sorts of "openness" in personality typology, behavior genetics, and the organic medicine of disease entities whose specific etiology and detailed pathology are not yet

fully worked out. They are as follows: in Carnap's meaning, this openness arised from the fact that the list of indicators (in the original Carnap terminology, the list of test conditions and test results for what he called "reduction pairs") is an open list, in that we do not rely upon only one definitive indicator; and when we do list them, we do not claim that the list is complete, because we expect more advanced knowledge to discover others in the future. This extendability of the indicator list is the first kind of conceptual openness.

A second kind of openness which Carnap did not consider but which Pap emphasized in his contribution is the probabilistic character of the linkage postulated to obtain between any one indicator and the disease that is being implicitly or contextually defined by the indicator list. In medicine this corresponds to our recognition that there are very few truly pathognomic signs, either in the sense of an inclusion test (one-way pathognomicity, where the presence of the sign quasi-proves the presence of the disease) or stronger, two-way pathognomicity, where the absence of the sign excludes the disease. An inclusion test rules in; an exclusion test rules out. A highly valid inclusion test corresponds to a low rate of so-called false positives in the terminology of medical technology and psychometrics; whereas a powerful exclusion test means that there are very few "false negatives," that is, cases in which the sign is absent but the disease truly present, nevertheless. A high-validity exclusion test, with a negligible false-negative rate (the absence of the quasi-pathognomic sign effectively rules out the disease) corresponds to the epidemiologist's concept of sensitivity; whereas a high-validity inclusion test, with a negligible incidence of false positives, corresponds to the epidemiologist's concept of specificity. Specificity equals the complement of false-positive rate. There are interesting relationships between these concepts in medicine, epidemiology, and psychometrics and the geneticist's concepts of expressivity and penetrance which are discussed briefly below.

A third kind of openness, which superoperationists (in psychopathology, superbehaviorists) tend to reject, I believe is extremely important in filling out either the psychological or the genetic model analogously to how general medicine has done so for many years in researching loosely identified diseases. In my classroom lectures on philosophical psychology, I call it "Orphan Annie's Eyes." As has become customary in contemporary philosophy of science, suppose one represents the system of theoretical factors and entities underlying our clinical observations as a network diagram in which the strands of the network correspond to postulated causal laws connecting various theoretical entities (states, structures, events, dispositions) that are jointly explanatory of the observations and the nodes in the network as (typically open) circles corresponding to these theoretical entities that are

related by these postulated laws. Then, even at advanced stages in our knowledge and certainly at the beginning when we have only a crude syndromic conception of a disease entity and hardly any conjectures as to its pathology or specific etiology, we do not know, so to speak, the "inner nature" of the postulated causal entities but only something about their mutual causal connections. The aim of our research into pathology and etiology is, however, to replace those open circles which are currently given their meaning (solely or mainly) by their role in the postulated theoretical explanatory system—that are, as some would say, implicitly or contextually defined by the nomological network itself (see Cronbach and Meehl 1955)—by explicit definitions. But these late-stage explicit definitions are not usually expressed in the observational language of the original (clinical) data base; rather, they are expressed in terms of the theoretical entities of a science lower in Comte's pyramid of the sciences. For instance, the concept "gene" is now explicitly defined in terms of the sequence of organic bases that constitutes a certain coded region of the double helix, whereas prior to the discoveries of modern physiological genetics, the gene had to be defined implicitly by the statistical facts of population genetics plus an identification of its position on the chromosome from linkage maps and so forth. My older readers will remember Little Orphan Annie in the comic strips of years ago, whose cartoonist for some reason preferred to picture this juvenile fascist with empty circles for the eyes; and I have the habit of referring to the research task in the ultimate goal of this third kind of openness of open concepts as "filling in Orphan Annie's Eyes."

An objection made by superoperationists in the old positivist tradition is that one cannot make a factual (synthetic, empirical) claim about a correlation or causal connection between the indicators and a postulated disease entity that is conjectured to produce them, unless the postulated entity is somehow "independently definable." This argument seems plausible—even obvious—from considerations of undergraduate logic; but it is mistaken. It is true that I cannot attach empirical meaning to a single sentence connecting only two terms such as "All crows are black," if being black is part of the definition of the word "crow." But that is not the situation here. When we have two or more synthetic sentences, each of which contains an observational term (such as a symptom) as well as sharing a low-order theoretical term (such as the vaguely conceptualized new disease entity D), then by conjoining the two sentences we can generate a third synthetic sentence that contains only the two observational terms. Each sentence taken by itself is synthetic, and it is a factual claim about disease D, despite the fact that disease D is so far understood only as being the conjectured underlying causative factor that gives rise to the symptoms and hence to their observed statistical correlation, that is, their compresence in the syndrome. The

richer such a network becomes, the more the network contributes to the contextual or implicit definition of the theoretical entities that occur in it, despite the fact that each of the single sentences attempts to make its own separate factual claim. There is nothing viciously circular or semantically empty in saying, roughly, "The reason that the symptoms s_1, s_2, s_3, . . . , s_k tend to occur together more than chance would allow and in certain typical patterns is that each of these symptoms is produced by a diseased condition within the body which I am calling D. I do not yet know much of anything about the 'inner nature' (etiology or tissue pathology) of D. That ignorance is precisely why I am engaged in a research program to find out about these matters! Nevertheless, what I *mean* by D is the whatever-it-is inner tissue condition and etiological factor, if specific, that gives rise to this cluster of symptoms." I daresay most clinicians engaged in research on a new disease entity would insist that this is a meaningful and fruitful way to think and that, if the logician or philosopher of science cannot provide an adequate formal reconstruction of that thinking, so much the worse for him. There is something terribly wrong with a philosophy of science which will not do that much justice to the way ongoing science actually works and with conspicuous success.

I shall throughout this paper permit myself a severe simplification on the dependent-variable side, by treating the clinical disease as an entity dichotomously present or absent, quantifying the probability of its presence but not quantifying its severity or expressing numerically the different indicator weights that might be attached diagnostically to the "output" components of the clinical syndrome. My justification for this oversimplification, other than the fact that one cannot do everything at once, is that nobody to my knowledge has any general mathematical solution for the unsimplified case. Some have proposed that canonical correlation fills the bill, but there is no showing that it does so, on either causal or statistical grounds; and I am persuaded that it does not. For most purposes, it is adequate to speak first of the patient as having or not having a certain disease and then to go on, from the standpoint of clinical management, to deal with the various aspects that the disease presents in this individual patient by methods which may or may not attack the specific etiology and, in fact, frequently do not. While the oversimplification of referring to the disease as "present" or "absent" will be relied on in proceeding through my series of explications, I shall have a few words to say later on about the directions in which we might move by way of improving on that oversimplification, especially in the loose syndromes studied in behavior genetics.

A second simplification, unavoidable when trying to explicate a vague notion by formal treatment, is conceiving a population of individuals together with a broad but not empty characterization of their cir-

37

cumstances (biological, social, economic, climatic—most importantly, the physical circumstances of interest to an epidemiologist or a nutritionist that bear on the specific etiology of the disease). I do not wish to impose any strong restrictions on the characterization of the population or its environment but merely say that we conceive some such population cum environment to be the empirical subject matter of our quantification. It goes without saying that the gene pool and its various internal properties (e.g., linkage) is taken to be part of the characterization of the population under study. As the philosopher J. L. Mackie explains (1965, p. 5), discussions in biological and social science presuppose a causal field, usually tacit. Thus a human being cannot develop Huntington's disease unless minimal survival conditions (nutrient, oxygen, shelter) permit his reaching the morbidity-risk age, but we would not ordinarily mention "adequate food" as one of the causal factors contributing to Huntington's disease. Similarly, we do not usually mention "exposure to language" when offering causal explanations of schizoid speech.

Taking the clinical disease as being either "present" or "absent" (although allowing for variation in severity as well as in the presence or absence of the several symptoms that make up the loose cluster called the "syndrome"), we conceive the probability of clinical illness as being a function of a set of variables, known and unknown, $x_1, x_2, \ldots, x_m$, and thus we write

$$p(D) = F(x_1, x_2, x_3, \ldots, x_m). \tag{1}$$

If we were complete determinists, which I am not assuming here, and if our knowledge were complete, then this function would be a deterministic expression, and for any choice of x-values $p(D)$ could have either of the two numerical values 1 or 0. I assume throughout that the function F (and other component functions written) refer to genuine dependencies; that is, we exclude the mathematician's special case where $F = k$ (i.e., its value does not change with changes in the variables).

If we do not postulate strict determinism in biological matters or if we postulate it metaphysically but assume that function F is incomplete, so that some aggregate of numerous minor influences contributes to the determination of disease but are left out of the equation of "major systematic causal factors," then for any particular configuration of the x's the equation yields a probability number lying between 1 and 0. The x's here include causal factors of all kinds including genetic predisposition, exposure to various microorganisms, diet, psychological stressors, and the like.

The clearest and strongest case of specific etiology, in which there would be no dispute as to the proper applicability of that expression if we allow the term at all (i.e., if there is ever a situation with specific etiology, this is it) is that of a factor which has a dichotomous, "present-

or-absent" character not arbitrarily set by drawing a cutting line on a quantitative dimension but by its very nature something qualitative, something that is either present or absent, which if present leads to the disease in all instances and in whose absence the disease cannot arise. That is, the presence of this causal factor is both necessary and sufficient for the disease to occur. An example would be a Mendelizing mutation of complete penetrance such as in Huntington's disease, where nobody falls ill of Huntington's disease unless he has that particular mutation at that locus, and everybody who has that mutation will develop the syndrome of Huntington's disease, provided he lives long enough. In that causal setup, we can rewrite general function F as a product function in which the first component of the product depends upon the mutation and the second component depends upon all of the modifying genes and environmental factors which determine, for instance, whether the individual becomes symptomatic at age thirty-five or at age forty-five. We know that, while Huntington's mutation is completely penetrant for those who survive the risk period, some people will die before they show the illness, and studies of sibships carrying the Huntington gene show a moderate to high correlation between sibs as to age of onset. We can write for this case (restricting the causal field to those surviving risk period)

$$p(D) = F(x_1, x_2, x_3, \ldots, x_m) = (x_1), \tag{2}$$

where $x_1 = 1$ if the gene is present and $x_1 = 0$ if the gene is absent.

More generally, recognizing that other variables than mere survival will exert an influence, we write, for a specific etiological factor x_1 which is necessary but not sufficient,

$$p(D) = F(x_1, x_2, \ldots, x_m) = (x_1) \cdot f(x_2, x_3, \ldots, x_m), \tag{3}$$

where there occur values of the $(x_2, x_3, \ldots, x_m)$ such that $f < 1.00$.

Of course when there is reason to extend the causal field by including chronological age as a significant variable, this can be done in equation (3). For Huntington's disease, we might then add the factual claim, if $x_2 = $ age, that $f \approx 1$ for $x_2 > 75$. Both the case represented in equation (2) and that in equation (3) might be labeled "specific qualitative etiology," since the specific etiological factor is dichotomously present or absent and is a necessary condition (sine qua non) for disease D. The difference between them is that (2) is the strong case, in which—given survival of the risk period—the etiological agent is both necessary and sufficient for the disease, and (3) is the weaker and commoner one, in which the specific etiology is a sine qua non but not sufficient without suitable combinations of those nonspecific contributory factors represented by the other variables $x_2, x_3, \ldots, x_m$ that appear in the equations.

Sometimes there is a factor that is not qualitative ("present-or-absent," such as a gene) but inherently quantitative or dimensional,

despite the fact that one may for convenience or administrative reasons locate a cutting score on it. This cut represents a human decision rather than two qualitative states of nature, and yet the agent behaves pseudoqualitatively and could be adequately represented, with only a small distortion of the quantitative relationships, by a dichotomy, because the dimensional variable exerts a so-called threshold effect. Here there is some value K of the crucial factor x_1 below which no combination (or at least no empirically realized combinations in the factor space) give rise to the disease, no matter how adverse and interactive they may be; whereas above that critical value K of the variable x_1 the disease has nonzero probability, these probabilities being again determined by the pattern of the other factors. We may call this, following the semantic habits of geneticists, "specific threshold etiology" and write it as follows:

$$p(D) = F(x_1, x_2, \ldots, x_m). \tag{4}$$
But if $x_1 < K$, $F = 0$ for all x_i-combinations, $i \neq 1$;
if $x_1 \geq K$, $F > 0$ for some x_i-combinations, $i \neq 1$.

This type reveals that, unfortunately, the "weaker" meanings of specific etiology are not factor unique, because one factor can operate as a sine qua non (eq. [3]) and a different factor as threshold (eqq. [3] and [4]). Examples would be the phenylketonuria (PKU) genotype (autosomal recessive homozygous condition as $x_1 = 1$) and the above-threshold intake of phenylalanine (environmental factor $x_2 > K$). I know of no way to define specific etiology that generates a unique factor except the unusual necessary-*and*-sufficient kind.

A still weaker form of specificity is that in which a causal factor exerts the greatest quantitative weight upon the probability of disease everywhere in the etiological factor space, which we may call the "uniformly most potent" factor kind of specific etiology. I suppose nutritionists would consider caloric intake as playing this role in the causation of obesity. Formally, we would represent that circumstance by the condition that, when disease probability $p(D)$ is examined as a function of small changes in any of the etiological factors that appear in the total etiological equation, it turns out that a small increment in factor x_1 makes a bigger difference than a small increment in any of the other factors would make and that this holds everywhere in the etiological space. There is of course a problem here about the metric. The least arbitrary way to set up the metric so that this kind of expression can convey the meaning we want is that all of the variables are expressed in standardized units representing normalization with respect to the variance of the distributions in the empirically realized space of causal influences. This might seem to make it a bit fuzzy, but actually it represents in the formalism the fact that whether one factor is uniformly most potent in producing an increment in disease probability is context dependent, so

that for a different gene pool or a different environmental surround a factor might lose out under this definition, which is what we want it to do. When the relevant variables have all been standardized (not around zero—they cannot be standardized there because of sign problems with the derivative—but, rather, around some other origin which makes them all positive), we can write as the condition for the uniformly most potent factor type of specific etiology the following, where we differentiate the probability function partially with respect to each of the variables and variable x_1 is the one that makes the biggest difference everywhere in the causal space,

$$\frac{\partial p}{\partial x_1} > \frac{\partial p}{\partial x_j} \text{ for all } j \neq 1, \text{ everywhere.} \tag{5}$$

Similar to specific threshold etiology because of the element of a "jump" or discontinuity but differing from it because we do not require in this next type that the probability of disease below the jump should be 0 is specific step function etiology. In this situation, there is one and only one variable in the set of x's such that the probability of disease shows either literally a step function (not likely to be strictly true in biology) or is characterized by a region of relatively sudden marked acceleration in disease probability, and then another region is relatively flat so that it can be characterized as "almost a step function." That is, we have only one causal factor which for some value or relatively narrow range of values that it takes on in the empirical causal space yields a marked increment in the disease probability, but it need not (and in general will not) do this anywhere else in the range of its own values, and none of the other factors that contribute to disease probability exhibit such a step-function influence. Formally we have

$F(x_1, x_2, \ldots , x_m)$ is a step function at $x_1 = K$ but is not a
step function for any x_j ($j \neq 1$) anywhere. $\tag{6}$

A rare case which I am not prepared to exemplify but which I suspect exists is that in which the specific etiological factor is identified by the fact that it "makes a difference" in the disease probability under the whole range of combinations of the other variables, but this statement is not true for any of the others, although there may be extended regions in the factor space for which one or more of the others exert considerable influence. When we get to this weakened a meaning, it is very doubtful whether the terminology "specific etiology" is appropriate. Formally we have that, if variable x_1 is the specific etiological factor, which in this weak case I shall call "uniquely ubiquepotent," meaning that x_1 is the only factor in the set which has an influence on the disease probability everywhere,

$\dfrac{\partial p}{\partial x_1} > 0$ for all $(x_2, x_3, x_4, \ldots, x_m)$, but this is false for any
variable x_j $(j \neq 1)$. (7)

This means that, if we take the partial derivative of disease probability $p(D)$ with respect to any variable x_j other than x_1, there will be combinations of values of the remaining variables $(x_1, x_2, x_3, x_4, \ldots)$ such that this partial derivative with respect to x_j is zero. In other words, there exist combinations of factors such that an increment in any *non*specific factor x_j $(j \neq 1)$ makes no difference. Factor x_1 matters everywhere, but nothing else does.

A meaning of special interest in behavior disorders such as schizophrenia because something close to it might apply is what I may call (following the terminology of lawyers) a "uniquely nonfungible factor" (where, as in legalese, a factor is "fungible" if it can be interchanged with another and make no significant difference). This is also an extremely weak case but is of great theoretical interest. Here we look at the upper (instead of the lower) end of the probability values; that is, we concern ourselves with what circumstances will make the probability of disease equal to one (or at least quasi-certain) rather than what will make it different from zero. Suppose that there is some factor x_1 which, when present to some degree (including the special case analogous to specific qualitative etiology and specific threshold etiology of its being nonzero, but the general case is for its having some fixed minimum value) assures that, for any *other* factor x_i $(i \neq 1)$, however disease resistant its value is chosen, some combination of the *remaining* factors $\langle x_j \rangle$ $(j \neq i)$ will produce the disease. But this is false for any other factor than x_1. We have, for our uniquely nonfungible factor,

If $x_1 > K$, then for any other $x_i(i \neq 1)$, however small x_i is taken, there are joint values $\langle x_j \rangle$ $(j \neq 1)$ such that $p(D) = F(x_1, x_2, \ldots, x_m) = 1$; but this is false for any other $x_i(i \neq 1)$. (8)

Where the nonfungibility comes into this setup is that one can, so to speak, "make up for" an extremely low (or perhaps even zero) value of any factor by choosing suitable joint values of the remaining factors, provided that the specific factor x_1 exceeds a certain critical value (again, conceivably, if it exceeds zero), so that all the other factors are mutually fungible in the sense that we can make up for one of them being very low (or even zero) by making the others sufficiently disease productive. But factor x_1 is not fungible, and it is the only one which is not fungible.

An example of this uniquely nonfungible kind of specific is Gottesman and Shields's (1972) polygenic theory of schizophrenia. They think of the conjectured polygenic system as determining an endophenotypic dimensional variable (inner trait) that is schizospecific, not something found also in, say, the affective psychoses, psychoneuroses, character

disorders, and the like. (I have some doubts as to whether this position can be made fully coherent, and my dialogue with Gottesman at Minnesota continues; one result of this dialogue we hope will be a joint paper on how the concepts of specific genetic etiology relate to the concepts of penetrance, expressivity, modification, and what I prefer to call "potentiation" in the genetic behavior disorders.) I shall here adopt one interpretation of the Gottesman-Shields position (which is among those that they would find acceptable until further notice, although not the only one definable within the general outlines of their etiological position). We imagine a set of genes that additively influence some schizospecific endophenotypic variable (e.g., a parameter of synaptic function), which latter interacts with various other endophenotypic variables, partly genetic and partly environmental in origin, such as social introversion, anxiety, dominance, intelligence, and the like. For simplicity, let me consider along with the schizospecific factor—the factor whose specific etiology is here to be formally defined—only two other factors, say, the malignity of the schizophrenogenic mother and the individual's polygenic social introversion. Of course neither Gottesman and Shields nor I hold any such simplistic view of the matter, the list of modifiers, potentiators, and environmental influences being surely longer than two variables in number—presumably at least as long and complicated as the list found in my monogene dominant theory (see Meehl 1972, p. 16) and including such factors as anxiety parameter, aggression parameter, sex drive, hedonic potential (Meehl 1975), energy level, mesomorphic toughness, dominance, and the like. But this rather special and, at first appearance, strange kind of specific etiological influence is almost impossible to explain in words without simplification to a small number of nonspecific contributory factors, and so I shall do it that way and rely upon the formalism of equation (8) to express the generalization to the case of more variables. In one plausible variant of the Gottesman-Shields model, what we imagine is that the polygenic schizospecific factor must be present to a certain minimal amount ("threshold value") in order for clinical schizophrenia to occur, and this aspect of the claim of specific etiology is covered by equation (4) supra. But now comes the more interesting aspect, which is not merely one of sine qua non but goes on to give a sufficient condition within a certain causal field. We have asked first whether $p(D) > 0$, but now we go on to ask what the conditions are for $p(D) \simeq 1$, approximate certainty of clinical disease. Suppose we now say that there is some value of the schizospecific polygenic factor—it need not be quantitatively the same as the value given as a sine qua non from the threshold standpoint—such that, no matter how favorable to mental health (hence modifying *downward* the probability of clinical schizophrenia) may be one's polygenically determined social extraversion, the direction here being more extraversion associated with less

43

schizophrenia likelihood, there is nevertheless, for any such disease-resisting amount of polygenic social-introversion factor, a sufficiently malignant-schizophrenogenic-mother factor to make it quasi-certain that one will develop schizophrenia. Similarly, no matter how nonhostile, nonambivalent, nonrejecting, loving, and supporting one's "good mother" may be, thus conducing to mental health and resisting the development of schizophrenia, there is some high value of social intro-version so extremely adverse as to potentiate schizophrenia with quasi certainty. That means that, considering these two nonspecific factors, polygenic social introversion as a heritable factor and schizophrenogenic-ity of mother as an environmental factor, either can be, so to speak, substituted for the other. A sufficiently adverse loading of one factor can "make up for" a favorable, counterschizophrenic loading on the other one enough to make quasi-certain the appearance of clinical disease. As regards precipitation of clinical schizophrenia, social introversion and battle-ax mother are fungible in their influence. But now suppose we say, with Gottesman and Shields, that the same is not true for the polygenic schizospecific factor; that is, there are sufficiently low values on this one that they cannot be made up for by sufficiently adverse pathology pro-ducing values of either or both of the other two. And suppose that the only causal factor in the system which is not fungible in the way that battle-ax mother and heritable social introversion are mutually fungible is the Gottesman-Shields schizospecific polygenic factor; then we say that this schizospecific factor is uniquely nonfungible with respect to quasi-certain clinical disease. This is a useful and causally interesting meaning of specific etiology importantly different from the sine qua non definition that operates at the low end of the disease-probability interval.

It is counterintuitive to speak of two "specific" etiologies for the same disease, yet we have difficulty seeing why either phenylalanine intake or the PKU genotype should receive privileged causal status over the other. I have elsewhere (Meehl 1972, p. 18) pointed out that a marked difference in a causal factor's frequency is commonly the (hidden) basis for such a semantic choice. The PKU genotype being extremely rare and suprathreshold amounts of phenylalanine being regularly found in "nor-mal diet," we elect to consider PKU a genetic disorder. When we contemplate examples such as death of spouse precipitating depression in a genetically predisposed person, the choice is harder and looks more arbitrary. But nothing substantive hinges upon the causal semantics as long as our usage is clear, consistent, and theoretically powerful. One terminological convention would be to label all of the foregoing kinds of dependency "strong etiologies" or, perhaps better, "strong influences" and then to confine "specific etiology" to the strongest (such as sine qua non). This seems closest to the traditional explicandum in medicine and genetics. Another possible rule would be to call them all "strong etiology

(or influence)'' and then, for each disease D, to designate the strongest causal dependency found for D as its specific etiology, provided it is far enough along in the series of strengths. Thus if the strongest kind of influence on D were, say, a threshold etiology, as in equation (4), there being no qualitative sine qua non like germ or gene, the threshold factor would be the specific etiology for D. (But suppose D has two such?) I have no terminological proposal to press here, except the generic ''strong etiology'' for the whole sequence of progressively weaker sorts of influence we have considered up to this point. Beyond that proposal, I think perhaps ''specific etiology'' should be confined to sine qua non and stronger (eq. [3]). We may upon reflection decide that multiple specific etiologies should be allowed and that our intuitive insistence on uniqueness is dispensable, but I hardly expect so. The cases to follow infra are so weak as not even to be candidates for the ''specific'' label, but they are still variants of strong influence and of considerable theoretical interest.

An important concept in psychometrics, originally from industrial and educational psychology, is that of a moderator variable. This is not the same as the geneticist's concept of modifier, although it has important relations to the latter both statistically and causally. We speak of a variable functioning in a prediction system as a moderator if a predictor variable relates differently to the outcome (to-be-predicted, ''criterion'') variable depending upon the value of the moderator variable. A familiar example of this in educational psychology is sex as a moderator of the predictability of academic achievement from intelligence test scores, in which it is regularly found that one can predict school grades for females more accurately than for males from the tested intelligence of the subjects. Since the predictability (usually represented by the Pearson correlation coefficient r) of academic achievement from measured intelligence is greater for females than males, sex is said to operate as a moderator variable in such a prediction system. In the present context, a factor x_i will be said to be x_j-moderative if the effect of x_j on the disease probability, say, $y = p(D)$, is itself a function of x_i. In terms of the general formalism we are using, we would write

$$\frac{\partial y}{\partial x_j} = \phi\ (x_i) \text{ for } some\ x_1, x_2, \ldots, x_m. \tag{9}$$

Given that definition of a factor as x_j-moderative, we can now define the concept of being x_j-ubique-moderative. A factor x_i is said to be x_j-ubique-moderative if it is x_j-moderative everywhere in the factor space; that is, the impact of an increment in factor x_j upon $y = p(D)$ is everywhere influenced by the level of x_i, which means that the x_j-ubique-moderative factor x_i everywhere influences the influence of x_j upon the disease probability. We have in the formalism

45

$$\frac{\partial y}{\partial x_j} = \phi\ (x_i) \text{ for all } x_i, x_2, \ldots, x_m. \tag{10}$$

Suppose further that there is factor x_i which has this ubique-moderative (second-order) influence upon the first-order influence of a factor x_j on the disease probability for all other factors j; in other words, factor x_i is ubique-moderative for each other x_j; then we say that factor x_i is omni-ubique-moderative. Factor x_i, so to speak, "potentiates" the impacts of all the other causal factors on the disease probability in all regions of the factor space, and we have in the formalism

$$\frac{\partial y}{\partial x_j} = \phi\ (x_i) \text{ for all } x_j \text{ at all points } x_1, x_2, \ldots, x_m. \tag{11}$$

Finally, it may be that factor x_i is the only factor which is a moderator variable everywhere in the space with respect to every other causal factor. That means that it is the only factor that is omni-ubique-moderative, so we may say that the factor x_i in that case is uniquely omni-ubique-moderative. That is, it moderates the influence of each other factor everywhere, and this is not true for any other factor. Then we have in the formalism both equation (11) just preceding and

$$\frac{\partial y}{\partial x_j} = K \text{ for some points } (x_1, x_2, \ldots, x_m) \text{ if } j \neq i. \tag{12}$$

In this connection, the reader may wish to consult a highly general definition of configural effects for prediction systems (which applies equally well for causal and retrospective analysis as to straight forecasting) presented in my book on actuarial prediction (Meehl 1954, p. 134; see also the general remarks on quantification of clinical material in the text associated with that equation).

Another interesting concept is that of the uniquely largest moderator, where a variable moderates the impact of another variable on the disease probability with a greater second-order effect on the latter's first-order influence more strongly than does any other variable (when they are expressed in appropriate standard score form) and this is true of this particular moderator variable with respect to all of the others. Formally we have

$$\frac{\partial y}{\partial x_j} = \phi\ (x_i) \tag{13}$$

and

$$\frac{\partial^2 y}{\partial x_i \partial x_j} > \frac{\partial^2 y}{\partial x_k \partial x_j} \text{ alone.} \tag{14}$$

I have not been successful in finding empirical examples to illustrate each of these meanings, although it is encouraging to discover that one's

medical or genetics colleagues sometimes find it easy to produce one on demand, once the formal definition of the particular type of specific etiology has been explained. But it would be counter to the purpose of a paper such as this, merely because an example does not readily come to mind, to exclude meanings that are formally possible and logically coherent and which make some prima facie sense in terms of our usual thinking about causality in the biological and social sciences. One presumed value in having such a list of formal explications is to direct our attention to the search for instances. This process has been fruitful in my own thinking about the theory of schizophrenia, because, in a trans-Atlantic exchange with Gottesman and Shields prior to the completion of the manuscript of their book (Gottesman and Shields 1972), I found myself developing one meaning for which I at first had no example and only subsequently have come to realize that it is a possible formalization of the Gottesman-Shields polygenic view. In the other sciences, it has sometimes been useful to reflect upon the failure of the empirical world to provide examples of something formally possible (e.g., theoretical crystallography, Dirac's "holes"), and if a mathematically definable and causally plausible sort of strong etiology has no empirical realization anywhere in genetics, medicine, or behavioral sciences that deal with psychopathology, then one is confronted with a problem of explaining why such a "gap" exists. I am not here asserting a negative thesis about any of the meanings explicated supra, and my personal conjecture is that they all have empirical exemplifications (allowing for the usual element of idealization and approximation). If a reader is distressed by the presence of one or more for which he can think of no factual realizations within medicine, genetics, or psychology, he should know that I would not view this, even if it turned out to be the case upon extended search and reflection, to be a compelling argument that this one of the formally conceivable kinds of specific etiology or strong etiology should be deleted from the list.

It may be asked what kind of causation there could be that is *not* covered by the preceding list, especially when the list is expanded to include various kinds of "privileged" or "prepotent" causal influences that are, despite their interesting and important special properties, surely too weak in the causal role to be called "specific etiology," if that phrase is to retain, when explicated by the formalism, something reasonably close to its traditional meaning in medicine. But as it happens, there is a kind of causation which does not, unless I am mistaken, satisfy any of the formal conditions in the list above or approach them closely and which turns out, surprisingly enough, to be so common a kind of causality in the biological and social sciences as to make one wonder upon reflection whether it may not even be the modal type. This is especially odd because the explication of this final kind of causation, which I am not including in the list above as even a "weak" meaning of specificity or

strongness but, on the contrary, am emphasizing as an important *non*specific etiology, was not explicated until about a decade ago. Although it is a nonspecific kind of causation, its ubiquity in biological and social science and my observation that very few physicians, geneticists, or psychologists have ever heard of it lead me to append it here in a summary fashion. The reader is referred to its expositor, J. L. Mackie (1965, 1974). It will be convenient to consider a nonmedical example which I think is quite noncontroversial as to the legitimacy of the word "cause," despite the nonspecificity and the fact that the attributed cause is neither a sufficient nor a necessary condition in the traditional sense. Suppose a fire burns down a factory and the arson squad suspiciously investigates, following which they issue a report stating that "the cause of this fire was a short circuit in fuse box B in the left wing." No one with either scientific or legal intentions would reject this as a meaningless assertion or as an unsatisfactory explanation of the fire. But how do we unpack it? Clearly the causal factor alleged in explanation of the fire is neither necessary nor sufficient, since everyone knows that a short in the fuse box does not always result in a factory burning down (because, e.g., there may be no flammable material near the box, as when it is attached to a concrete wall with no wooden ceiling; or affirmatively there may be a preventive factor such as an adequate sprinkler system in that wing). Nor does anyone argue that this causal agent is a necessary condition for such a factory fire, since it could have been started (as the squad suspected) by arson, by spontaneous combustion of some old rags in the basement, by lightning, and so on. Without going into the details which are so lucidly set forth by Mackie, I simply state here his earlier (1965) formulation, warning the reader that he modifies it and clarifies it in the book chapter (1974) cited, but for present purposes the easier 1965 formulation is adequate. The essential feature of Mackie's explication is that the event we focus upon as "the cause" of the factory fire, here the particular event of the short circuit in the particular fuse box in which it happened, is part of a complex of circumstances prevailing in the factory at that time, both affirmative and negative, such that, if the other elements of the complex are imagined to be held fixed, that is, to have been as they in fact were, then a fire would not have occurred if there had not been the short in the fuse box; but, on the other hand, *given* the rest of the complex *being as it was*, the fire did necessarily occur because there was this short in the fuse box. So the event we are labeling "the cause" for arson-squad purposes, to wit, the short in the fuse box, while it would not be a sufficient condition for the factory fire unless certain other conditions had been satisfied, was sufficient, given that those other conditions were satisfied; and the total complex of compresent conditions of which it is a part makes the fire necessary, that is, is a sufficient cause for the fire. So we say in words S, "A causal factor *c* may be an

insufficient but necessary part of a causal complex C, which complex is an unnecessary but sufficient condition for producing the effect." What is sufficient is the entire complex of circumstances. That is, if there is no sprinkler system and no night watchman and there is some flammable material near the fuse box and . . . , *then* the occurrence of a short in the fuse box B in the left wing will guarantee that the factory burns. On the other hand, this whole complex is not the only way to have a factory fire, so the complex is, as a complex, not necessary. The fuse-box short is not by itself sufficient, since certain other features of the complex are required to be present for it to result in a fire; but given those other positive and negative conditions, a fire would not have occurred unless there were this event. So what we have in such cases is a rather long list of complexes, that is, a *dis*junction of *con*junctions of positive and negative conditions. When the complex that was actually realized among this disjunction of complexes, each of which is a conjunction of conditions, includes a particular condition whose absence from that disjunct would have made the fire impossible but whose presence, given the other conjuncts in the realized disjunct, made it inevitable, this factor that was operative in the actually realized member of the set of possible causal complexes is referred to as an INUS condition, the acronym "INUS" being formed by the initial letters of the words "insufficient," "necessary," "unnecessary, and "sufficient" in complicated sentence S supra. A medical example would be the claim on a death certificate that patient Jones died of coronary occlusion following a bout of excessive jogging, which is certainly a meaningful statement (although it might be difficult to confirm in a given instance, which is not the issue here) but which does not say that the only way you can die is by coronary attack; nor does it say that the only way you can bring on a coronary attack is by an excessive bout of jogging. Yet given all the other circumstances of this man's physical condition and the temperature of the summer day and so on and so forth, this particular excessive bout of jogging was an INUS condition for the coronary attack, which was an INUS condition for his demise. I think reflection will convince the reader that INUS conditions, despite the novelty and complexity of the notion as Mackie has expounded it for us, is not an esoteric, oddball, rare kind of causal explanation but, on the contrary, is one that occurs with extreme frequency and, as I suggested above, perhaps the modal type of both medical and social science. It is not an example of specific etiology, in my explicatory proposals.

When we abandon the simplifying notion of the disease entity being simply present or absent, which allowed the definitions of specific etiology to be formalized in terms of functions with a single quantity, $p(D) = $ "probability of disease," as the dependent variable and consider more realistically the causal and statistical situation in which the various

antecedent factors that appear in the probability functions "fan out" on the input (causal) side and another set of variables "fan out" on the output side as traits, signs, symptoms, residuals, prognostic variables, and the like, then I do not have even a hint of a general solution; and what hazy ideas of a nonmathematical sort I have cannot be discussed here within my space limitations. I therefore permit myself only some remarks about the increasingly important field of loose syndromes in behavior genetics such as manic depression or schizophrenia or sociopathy of the constitutional variety, where I am convinced that traditional modes of thinking about modifiers, penetrance, and expressivity are misleading and should be critically examined for these kinds of situations. Considering the statistical and causal situation that obtains for loose syndromes in behavior genetics, I argue that expressivity rather than penetrance should be taken as the basic scientific construct and that there are as many expressivity functions as there are phenotypic indicators of the loose entity. For a given genome-cum-environment joint distribution, a soft neurological sign of the schizotaxic CNS (central nervous system) effect (postulated in my theory [Meehl 1962, 1972]) has a certain expressivity function which is a fact of the state of nature; similarly, a deficiency in hedonic capacity, in verbal associative control, of "basic oral trust," or whatever other psychological or neurological variable belongs even peripherally to the "schizotypal cluster," each has its own expressivity function. The quantitative distribution of any one of these characteristics is, on a dominant-gene hypothesis, the same whether the patient is heterozygous or homozygously schizotypal; and this distribution overlaps with the distribution for the homozygous normal type. There is nothing arbitrary about this expressivity function or about its overlap statistics with the normal. Given a specified base rate P for schizotaxia and specified disutilities for the two kinds of errors, an optimal cut is determined. Straight "least misses" rule defines a "hitmax cut" as the intersection of the normal and deviant expressivity functions unrelativized as to P (see Meehl 1973), if we were diagnosing genotype by one indicator alone, which in general would not be wise. It is obvious that, for each of these phenotypic indicator variables, the only situation in which the concept of penetrance can be other than an arbitrary cutting score, where we manipulate the ratio of false positives to false negatives for some administrative or clinical reason, is that in which the particular indicator is two-way pathognomic. In these behavior-genetics loose syndromes this never happens or at least is not known to happen for any indicator we have been thus far able to discover. (I do not of course rule out the possibility of some day, even in the near future, finding an endophenotypic indicator such as a biochemical trait, in which the expressivity functions would have zero overlap.) For further discussion of

the arbitrary character of the penetrance concept and the fact that there are as many penetrance coefficients as there are cutting scores on the set of fallible indicators, the reader is referred to chapter 12, "MAXCOV-HITMAX," in Meehl (1973) and the paper in preparation by Gottesman and myself.

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In summary, a disease entity is initially defined implicitly or contextually, loosely and not strictly "operationally," by the researcher-clinician's presenting a cluster of symptoms, complaints, and signs that covary over the population of patients (and usually over time in the individual patient). This observational finding suggests the conjecture that the cluster, usually called the "syndrome," exhibits its statistical togetherness because of a causal source shared in common by the several indicators. At this early stage of knowledge, the disease entity is an "open concept," in the philosopher's sense. The postulated causal relationships between the conjectured etiology and each of the fallible indicators provide *at one and the same time* a set of synthetic factual claims about the way the world is and, paradoxically, the implicit contextual definition of the entity. Three aspects of the openness of these concepts are discussed, to wit, (1) the extensibility of the indicator list, (2) the probabilistic rather than strictly nomological correlation between the indicators and the disease entity, and (3) "Orphan Annie's eyes," that is, the to-be-researched inner nature of the entity (as we expect it to be reduced to lower levels in the pyramid of sciences). An arbitrariness as to deciding for presence or absence of the syndrome in individual patients arises from the fact that the pair-wise relationships of the syndrome elements are typically imperfect correlations, which in turn arises because each of them is only a fallible (nonpathognomic) indicator of the latent pathological situation. We expect a disease entity to become defined jointly by the pathology and etiology when these become known, and we recognize that it cannot be defined explicitly (or "operationally") until that advanced state of knowledge has been achieved. A series of progressively weaker meanings of the expression "specific etiology" is set out without a claim to completeness or present exemplification of all of them in genetics, psychopathology, or medicine. Some related dependencies of a similar kind ("strong etiology") but too weak for labeling "specific etiology" are also developed. Finally, in the field of behavior genetics it is suggested that the expressivity function of each phenotypic element in the loose cluster should be taken as the basic quantitative concept, with penetrance being a derivative notion, one which is an arbitrary cutting score on each indicator in all instances except when the expressivity functions have zero overlap.

51

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53