

The End of Diseases

Marc Lange
University of North Carolina, Chapel Hill

I. INTRODUCTION

Disease categories have long been central to medicine. Malaria, tuberculosis, cancer, asthma, hemophilia, the common cold, congestive heart failure, gout, influenza, measles, syphilis, rickets, diabetes mellitus, lupus erythematosus, and emphysema—all have been considered types of disease. Recently, two physicians asserted that the question “What *disease* does this patient have and how do I *treat* it?” is a common statement of what “was, is, and will be” the “primary question in the practice of medicine” (Scriver and Childs 1989, 3). “Was” and “is”—yes. But not “will be.” The purpose of this paper is to understand the role that disease categories have long played in medicine and the reason that disease categories are now becoming obsolete.

Those who study medical thinking have typically regarded the distinction between diseases and other medical categories (such as injuries) as a folk distinction (or a historical artifact of the original distinction between physicians and surgeons) playing no role in scientific reasoning. As we will see, they have also generally considered individual diseases (such as those I have just listed) as functioning in medical thinking quite unlike the elements do in chemistry or even the species do in biology. Yet medicine itself appears to give great prominence to individual diseases. A glance at virtually any medical journal reveals scores of articles reporting research concerning specific diseases, with titles like “Elevated plasma chemokine CCL18/PARC in β -thalassemia” (Dimitriou et al. 2005) and “Frequency and

significance of granulomas in a cohort of incident cases of Crohn's disease" (Heresbach et al. 2005). The individuation of disease categories appears to be a chief medical concern. For example, the journal *Schizophrenia Research* recently devoted the first in its "Current Controversies" series to "whether schizophrenia is composed of multiple disorders with a common core clinical syndrome, or one disorder with variations in clinical presentation" (DeLisi and Nasrallah 1995, 133).

Accordingly, I shall argue that disease categories have functioned as medical natural kinds. Of course, that is not to say that the distinction between diseases and other medical conditions (or between having and not having a particular disease) is discontinuous, any more than there is a sharp distinction between deep and superficial scientific explanations.

I shall argue that a condition qualifies more fully as a distinct disease insofar as it is a natural kind of incapacity that figures in interesting function-analytic explanations of other, unhealthful incapacities. Whereas the philosophical literature has been preoccupied with understanding health (either naturalistically or in irreducibly normative terms or as relative to cultural expectations), I shall largely bracket this notion on the grounds that it plays no role in the scientific investigation of diseases. The belief that some condition contributes to health (or lack of health) makes no difference to the way that biomedical scientists investigate its causes and effects, for example (though it may well affect the funding they receive and the way that their discoveries are applied). I shall (i) argue that diseases are incapacities rather than states or processes, (ii) identify a disease's explanatory role and the constraints it imposes on what diseases can be, and (iii) offer an account of the individuation of diseases. Again, my proposal will imply that there are various sorts of intermediate cases. But in having these implications, just as in implying certain cases to be clear-cut, my proposal is responsible for according with medical practice and our pretheoretic intuitions (or for explaining why those intuitions disagree with medical practice).

In sections 2–6, my subject will be the notion of a disease as it has traditionally functioned in medical science. However, in the final section, I shall argue that genomic medicine—and molecular medicine more generally—will lead (in a matter of decades, I suspect) to the end of diseases as medical natural kinds. Although people will still be afflicted with diseases and disease categories will remain natural kinds, diseases will be called upon less and less to serve as natural kinds in medical reasoning. I shall explain why.

II. DISEASES AS MEDICAL NATURAL KINDS

Medicine aims to identify the disease(s) afflicting a patient. Such a diagnosis is intended to *explain* the patient's signs and symptoms. Therefore, a disease category must have "validity" (in the medical sense), which means that the disease must be a natural kind rather than an arbitrary category:

Psychiatric diagnosis enables a wealth of facts regarding a patient's history and current state to be communicated in just a word or two. But we ask more of diagnosis than efficient communication. We want it to be valid, by which we mean that we want it to correspond to what exists in nature—to describe a 'real' disorder. . . . The trick is to find indirect indicators that a diagnostic definition maps closely on to the "real" underlying disorder. (Robins and Barrett 1989, v)

Not all diagnoses are diseases. A fractured rib, for example, might explain the patient's symptoms, but it is not a disease; it is an injury. Other diagnostic categories purport to tell us something important about the explanation of various signs and symptoms, and may suffice for prognostic and therapeutic purposes, but are neither diseases nor natural kinds. For example, many diagnostic terms (such as otitis media, meningitis, pleurisy, sinusitis, glossitis, peritonitis, appendicitis, cholangitis, dermatitis, and bronchitis) denote the infection, irritation, or inflammation of some body part, regardless of the virus, bacterium, fungus, mechanical irritant, injury, gene, or chemical responsible. Some diagnostic terms convey little explanatory information because they merely cover what's left over after all known specific diseases of some sort have been subtracted; they are artificial categories, awaiting cleavage at their joints.¹

Physicians use inference to the best explanation to justify positing a new disease category. The fact being explained may be a single distinctive sign or symptom, as when Følling (1934) posited "an anomaly of metabolism, so far unknown" (later named "phenylketonuria") to explain the distinctive presence of phenylpyruvic acid in the urine of certain patients with mental deficits. The clinical feature needing to be explained (e.g., what Herrick [1910, 517] refers to as "the unusual blood findings, no duplicate of which I have ever seen described") is distinct from the new disease being posited as explaining it (sickle-cell anemia, in Herrick's case). Herrick's article plainly takes the form of an inference to the best explanation. He canvasses alternative possible explanations:

Syphilis is suggested by many of the facts, such as adenopathy and the condition of the heart and kidneys; it might explain the anemia, the arthritis and perhaps also the temperature, cough and attacks of pain . . . The patient coming from the tropics, one thought of intestinal parasites such as uncinaria as a possible explanation of the anemia and the eosinophilia. (1910, 520–21)

Having found difficulties with each of these alternatives, Herrick floats a more exciting possible explanation:

Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. (1910, 517)

Instead of explaining a single distinctive clinical finding, a disease might be posited to explain a syndrome (i.e., a distinctive group of signs and symptoms), as Osler's

(1903) title announces: "Chronic Cyanosis, with Polycythaemia and enlarged spleen: a new clinical entity." Osler refers to the clinical picture as "certainly very distinctive" and concludes, "Future investigation will determine whether we have here in reality a new disease" (1903, 201).

For a patient's disease to explain her signs and symptoms, the disease must be distinct from its clinical picture, since otherwise physicians would be calling upon that picture to explain itself.² Likewise, if having the disease were nothing but exhibiting enough signs and symptoms from a certain broad category, then the disease would not be explanatory; that Jones exhibits two or more of symptoms A, B, and C fails to explain why Jones exhibits symptom A. Sometimes physicians confuse the diagnostic criteria for a disease with a definition of the disease, mistakenly supposing that in good science, theoretical terms must be defined operationally. Kendell apparently intends to be putting the study of schizophrenia on a rigorous basis, rather than singling out schizophrenia as failing to constitute a natural kind, when he writes,

We are just using words like schizophrenia as a convenient shorthand for what would otherwise be a statement running to two paragraphs about combinations of symptoms. There is no such thing as schizophrenia. It is just a shorthand symbol. (1989, 323)

If Kendell were correct, then as the diagnostic criteria for schizophrenia have been refined over successive editions of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, the same disease has not remained under discussion.³

The inference-to-the-best-explanation argument for a distinct disease category is strengthened by finding more for the posited disease to explain: not only a distinctive clinical picture, but also a distinctive therapeutic response, a distinctive course or outcome, familial predisposition,⁴ or association with other features. For instance, that bipolar disorder responds to lithium salts, which have little effect on other individuals, is a powerful argument for the disease's reality (Cade 1949).

Sometimes it is discovered that what had hitherto been considered a single disease is actually several diseases instead, as when Sydenham discovered that "the pox" includes smallpox and measles. On other occasions, what had been regarded as distinct diseases are revealed to be a single disease instead, as when Koch discovered that phthisis (involving the lungs), scrofula (involving the lymph glands of the neck), Pott's disease (involving the spine), and others are all tuberculosis since they all are caused by infection with the same bacillus:

At first sight, however different the forms of lung-phthisis, acute and chronic military tuberculosis, the affections of the glands and mucous membrane under the general figure of scrofula, tuberculosis of the bones and joints, of localized tuberculosis of single organs, as for example the kidneys and the intestines, may appear, we shall see without difficulty that they belong together when we look at their mode of formation. (Koch 1884, 221)

Sometimes new diseases are recognized that had not ever afflicted anyone until relatively shortly before. Silicosis, for instance, presumably did not afflict anyone before industrial techniques exposed workers to silica dust, and no one contracted Legionnaires' disease before the microbe responsible for it came into being. Endstage renal disease did not exist until dialysis allowed patients without functioning kidneys to survive (Peitzman 1992, 15). Sometimes what had been regarded as a disease is discovered to be merely a symptom (such as fever, pleurisy, jaundice, or angina) because it is unable to do a disease's explanatory work (Bartlett 1844, 115).

Apparently, then, one goal of medicine has been to identify the real diseases. Just as two geological samples tend to share certain properties because they are samples of the same mineral, so two patients tend to share certain properties because they have the same disease. One patient's response to a given therapy is (*ceteris paribus*) made relevant confirmation-wise to predicting another patient's response by the fact that the two patients have the same disease.⁵ Diseases have functioned as natural kinds in medical reasoning.

This claim has often been rejected. Crookshank (1956), Cunningham (1992), Kendell (1975), King (1954), Reznick (1987), Scadding (1996), Wulff (1984), and Wulff et al. (1990, 77–88) say that diseases are useful categories but are not real in the same manner as, for example, the chemical elements. However, this view is typically defended only by slogans (“There are no diseases, only sick people”) and inadequate considerations: every sick patient is different, current medical knowledge is incomplete, “there is no natural dividing line between normal and abnormal [blood] pressures” (Oldham et al. 1960, 1085).⁶ After all, nitrogen atoms differ, too, in various respects (number of neutrons, kinetic energy, location), but nitrogen is a natural kind—and was even before nitrogen was discovered (cf. Bartlett 1844, 119, 124). Furthermore, as Sober (1980, 166) has remarked, there is no specific moment at which a nitrogen atom and an approaching proton become an oxygen nucleus. A natural kind need not have a sharp boundary. Moreover, that no one had endstage renal disease before dialysis was invented does not preclude its qualifying as a natural kind, just as a given chemical species (e.g., nylon) is a natural kind even though none existed before human beings discovered how to synthesize it.⁷ The role that diseases have been called upon to play in medical reasoning is much like the role that other natural kinds (such as the chemical elements) play in their domains. So there seems to be a good case for interpreting medicine as having treated diseases as natural kinds.

III. FOUR QUESTIONS ABOUT DISEASES

Why does a given disease (e.g., phenylketonuria) constitute a way of being unwell? Philosophers have examined extensively the distinction between being healthy and being unwell—especially whether unwellness is departure from statistically normal

functioning, or reduction of evolutionary fitness, or interference with human flourishing understood in irreducibly normative terms, or deviation from prevailing cultural ideals, or personal preference for medical intervention.

The question "What makes phenylketonuria count as a departure from health?" should be distinguished from another question, of a sort that has received somewhat less attention: What makes all phenylketonurics qualify as having the same disease? An account might explain why phenylketonuria is one disease rather than many without explaining why phenylketonurics count as unwell, or vice versa. There might be a natural distinction among diseases but not between being healthy and lacking good health, or vice versa.

The question "What facts determine whether phenylketonuria is a single disease or encompasses (aspects of) several?" is in some respects analogous to the question "What facts determine whether lions form one biological species or belong to several?" Diseases have often been compared to biological species (most famously by Sydenham 1676, 13). However, although a category broader than a given biological species is not itself a species, a category broader than a given disease may also be a specific disease. For example, emphysema and alpha 1-antitrypsin deficiency related emphysema may both be diseases. Medical reasoning could presuppose a natural hierarchy of such kinds even if diseases occupy many levels of the hierarchy.

The facts making phenylketonuria a single disease rather than (aspects of) several need not answer a third question: Why is phenylketonuria a *medical* natural kind? Phenylketonuria could be a distinct natural kind without being relevant to medicine, just as granite, diamond, muon, and red-giant star presumably are. Indeed, I shall ultimately argue that diseases, though genuine natural kinds, will be called upon less and less by medicine to serve as natural kinds.

A fourth question concerning phenylketonuria asks what makes it a disease rather than some other sort of medical category. As Reznick (1987) emphasizes, not all diagnoses are diseases, and diseases must also be distinguished from symptoms (e.g., fever), signs (e.g., Babinski's sign), syndromes, and anatomical variants (e.g., flat feet, a.k.a. pes planus). Myocardial infarction (death of heart muscle from sudden blockage of a coronary artery) is an event, not a disease. Injuries, wounds, swelling, allergies, disabilities (blindness, color-blindness), impairments (myopia), congenital malformations (cleft palate), anatomical lesions (subdural haematoma), poisonings, burns, starvation, and drowning are not widely considered diseases. (See the survey conducted by Campbell et al. 1979.) From the fact that mauling by a lion is not a disease but *Streptococcus pneumoniae* infection is (and other such examples), Reznick (1987) and King (1984, 167) conclude that no natural distinction exists between diseases and other pathological categories.⁸ We shall have to see whether (as King says) a disease differs in no important respect from an automobile accident or a bullet wound.

Of these four questions about diseases, I shall focus primarily on answering the second (concerning the individuation of disease categories). An answer to the

fourth question (on how diseases are distinguished from other medical categories) will follow as a corollary. The final section will take up the third question (regarding the conditions under which diseases constitute *medical* natural kinds).

IV. ETIOLOGY AS INDIVIDUATING DISEASES

Plausibly, etiology unites various tokens of the same disease and differentiates them from tokens of other diseases. Infectious diseases are paradigmatic. Since different microbes cause measles and smallpox, they are different diseases (though Sydenham's evidence for this distinction was entirely clinical). Phthisis and scrofula are both tuberculosis because the same microbe is responsible for both. Likewise, says Putnam,

When a patient has these symptoms we say he has "multiple sclerosis"—but, of course, we are prepared to say that we were mistaken if the etiology turns out to have been abnormal. And we are prepared to classify sicknesses as cases of multiple sclerosis, even if the symptoms are rather deviant, if it turns out that the *underlying condition* was the virus that causes multiple sclerosis, and that the deviancy in the symptoms was, say, random variation. (1975, 310–11)

However, different diseases can have the same cause. For example, exposure to cigarette smoke causes cancer and also causes emphysema. Cat bites can cause rabies, cat-scratch disease (infection by *Bartonella henselae*, a bacterium that is carried in cat saliva), and serious injuries that are not diseases at all. Depending on how coarsely we distinguish causes, we might even say that all genetic diseases have the same cause (namely, genes) and that a sedentary lifestyle is a cause of many diseases. Moreover, the same disease can have different causes. Some cases of rickets are caused by insufficient dietary vitamin D, others by an inborn error in renal synthesis of the hormone calcitriol, and still others by inherited disorders of renal phosphate transport. Some cases of emphysema are caused by exposure to cigarette smoke, whereas others are caused by alpha 1-antitrypsin deficiency (from a mutation on the long arm of chromosome 14); some are caused by both. Depending upon how finely we distinguish causes, we might even say that some cases of emphysema are caused by cigarette smoking whereas others are caused by second-hand smoke. Of course, neither all cancer nor all emphysema is caused by cigarette smoke. But even if there exists a cause that is common to all and only cancers, and another common to all and only cases of emphysema, there remains a cause (exposure to cigarette smoke) that is common to some cancers and some cases of emphysema, yet fails to unite them into a single disease.

Although etiology is surely crucial to disease individuation, it is not obvious how to elaborate the idea that "same cause = same disease." Tokens of the same disease must have causes that are similar in which respects? How similar? How remote

or proximate must the similar causes be? Are diseases individuated by their symptoms's causes or by their own causes?⁹ We also have to distinguish between "a cause" and "the cause" in making precise the notion that diseases are individuated by their causes. A disease could have a genetic contribution as well as some precipitating event, and a microbe could arrive in a patient's body but remain dormant until some stress weakens the patient's immune system.

Whitbeck (1976, 130) contends that "[t]he etiology of diseases is now accorded such importance that the preferred model of classifying a disease is in terms of 'the' object which causes it, its so-called 'etiologic agent.'" She recognizes the difficulties I have just mentioned, arguing that in "our preferred mode of classifying diseases," *the* etiological agent is distinguished from other causes by being proximate rather than remote and by being a factor existing in the environment prior to contact with the patient's body (1977, 631). However, this will not do.¹⁰ Consider an infectious microbe that enters a patient's body and then produces a toxic chemical (as in tetanus and cholera). Whitbeck says that the disease is individuated by the microbe rather than the toxin, since the microbe exists in the environment prior to contact, but the toxin does not. However, Whitbeck's criteria for *the* etiological agent fail to give a univocal verdict, since the toxin is a more proximate cause than the microbe. (Indeed, I am inclined to think that a patient who received tetanospasmin from an injection, rather than from infection by *Clostridium tetani*, would have tetanus.) Furthermore, Whitbeck (1977, 632) argues that genetic diseases accord with her account because a gene responsible for some disease was in the environment prior to "contact" with the patient's body, since it was in one of the patient's parents. However, this is not always the case with chromosomal diseases; in a Down syndrome mosaic, for example, the extra chromosome 21 results from nondisjunction occurring in an early embryonic cell division.

In short, although there is presumably something correct in "same cause = same disease," it is not evident what should qualify as the "same cause." This difficulty is not always appreciated. Klerman et al. (1987, 4) call evidence regarding etiology "conclusive" in establishing "the validity of a diagnostic class." Likewise,

The vexing problem is that we do not, in general, know the etiology or pathophysiology necessary for the development of a psychiatric disorder. One could take a purely descriptive or syndromatological approach, eschew etiological speculations, and simply advance the belief that certain combinations of manifest symptoms, associated with particular demographic characteristics . . . define a clinical picture worth attending to. The problem with this approach is that indefinitely many syndromes can be imaginatively stipulated. . . . We need validity criteria to decide which syndromes are likely to reflect relatively uniform pathophysiology and, hopefully, etiologies. (Klein 1989, 203)

Fair enough—but just as token combinations of symptoms can be grouped in various ways, not all of which correspond to real diseases, so token etiologies can be grouped in various ways, not all of which correspond to real diseases.

V. TO WHAT ONTOLOGICAL CATEGORY DO DISEASES BELONG?

To understand how etiology individuates diseases, let's consider what kind of thing we are trying to individuate. A disease—is it a process, a state, or an incapacity? (Of course, there may be other candidates as well.) If we understand the general ontological category to which a disease belongs, then we may be better able to see what aspects of a disease's etiology are essential to it.

All three—process, state, and incapacity—are *prima facie* plausible characterizations of what diseases are. Mitral stenosis might be a state: having a narrow outflow path from the mitral valve (between the left atrium and ventricle), or perhaps having mitral valve leaflets that are thickened, commissures that are fused, and chordae tendineae that are thickened and shortened. Or mitral stenosis might be a process: the gradual narrowing of the valve orifice, or the progressive thickening and calcification of the leaflets and chordae. Alternatively, mitral stenosis might be an incapacity: the valve's inability to open enough to permit adequate transmitral flow. Perhaps "mitral stenosis" can denote any of these. (It would not follow that in all these cases, it denotes a disease.)

Of course, it may be that some diseases are processes, others are states, and still others are incapacities. To avoid (or, at least, to defer) hasty generalization, I shall ultimately focus primarily on a single disease and ask: What is classical phenylketonuria (PKU)?

Consider first the view that "disease entities are complex processes not types of bodies" (Whitbeck 1977, 619). Whitbeck's opinion is shared by Reznek (1987, 71–3), Susser (1973, 4–5), Temkin (1977, 445), Thagard (1999, 155), Wiggins and Schwartz (1994, 98), and Wulff et al. (1990, 81). A common argument for this view is that a disease has a characteristic course and prognosis, can be diagnosed "early" or "late," has an "onset," and may "progress" through various "stages." However, this is a weak argument (just as it would be unconvincing to argue, from the fact that many diseases can be "mild" or "severe," that a disease is a kind of bodily state). All of these disease characterizations would be equally apt even if diseases were states or incapacities. A disease's onset, for instance, would be when the state or incapacity arises, and its prognosis would be its predicted result. The disease's progress would involve the temporal sequence of pathological bodily changes resulting from the persistence of the disease's distinctive state or incapacity. Admittedly, the disease's distinctive state or incapacity would not then be changing, but the regular sequence of resulting pathological changes in other bodily states or capacities could nevertheless reasonably be characterized loosely as "stages of the disease." This sequence is near its end in an "advanced case" and will soon be so in one that is "progressing rapidly." Likewise, a disease can get better or worse whether it is a state, process, or incapacity.

Another common argument (e.g., Whitbeck 1977, 625; 1978, 210) for interpreting diseases as processes is that diseases are thereby distinguished from injuries,

burns, deformities, anatomical lesions, and wounds, which are states, as well as from impairments, which are incapacities. However, as Reznick (1987, 73) notes, some pathological processes (such as drowning and starvation) are not diseases. For that matter, injuries, burns, and so forth would be excluded from the ranks of diseases even if diseases were incapacities rather than processes.

Another possible argument (after Virchow; see Englehardt 1984, 181) notes that diphtheria bacilli, for example, can exist in the throat of a healthy child. Until they initiate a certain sort of process, there is no disease (though a physician might nevertheless treat their presence prophylactically). However, this argument does little beyond ruling out the view that diphtheria is the presence of diphtheria bacilli. That diphtheria is some other state (or some incapacity) is not ruled out.

A more promising argument is that no state is common to all of a disease's stages, whereas all are parts of the same process (understood roughly as a sequence of causally related events).¹¹ We will consider shortly whether each disease category corresponds to a particular natural kind of state. But this argument highlights two difficulties with construing a disease as a process: (i) this view finds it difficult to account for the disease's explanatory role, and (ii) a disease can be present without any pathological process at all.

(i): If various symptoms and states are *parts* of the process that *is* the disease, then they cannot be *explained* by the disease, which conflicts with an important role that diseases play in medicine (see section 2). Of course, one stage of a process might cause a later stage, and a process may explain effects that remain after the process has ended (e.g., a childhood episode of rheumatic fever could explain an adult's residual heart damage). But if the disease is the process as a whole, then it cannot explain any of its parts. Whitbeck (1977, 632) elaborates this problem and replies that a disease, though a process, can nevertheless explain one of its parts because "classification using a *natural* classification frequently serves an explanatory function" (634). However, it seems to me, even such an explanation must conform to the requirement of noncircularity. If being disposed to exhibit a yellow flame when burned were part of what it is to be a sodium salt, then the fact that some sample is a sodium salt could not explain why it is so disposed.¹²

(ii): Someone can have classical PKU without any pathological process occurring. Classical PKU is an inherited (autosomal recessive) disease whose characteristic symptoms (notably impaired cognition, microcephaly, and motor dysfunction) and signs (phenylpyruvic acid in blood and urine, a distinctive "mousy" odor) result from elevated levels of L-phenylalanine (an essential amino acid) and some of its metabolic derivatives in bodily fluids and tissues. Phenylketonurics who do not eat any phenylalanine (phe) do not have elevated phe levels or any other PKU symptoms.¹³ Nowadays, infants are routinely screened at birth for PKU, and if they are found to have classical PKU, they are put on a phe-free diet for the remainder of their lives.

Let me emphasize this point. As I shall explain further, someone who is deficient in a certain enzyme necessary for phe metabolism has classical PKU—even if

no pathological process has begun because she has not eaten any phe. It is not the case that eating phe is required for having the disease. For instance, it is said that a child of two carriers has a 25 percent chance of having classical PKU. That percentage is not the likelihood of some pathological process since it does not reflect the likelihood that a child will be put on a phe-free diet. Likewise, it is said that the rate of PKU is different in different ethnic groups (e.g., 1 in 2,600 Turks, 1 in 143,000 Japanese). Once again, this is not the rate at which some pathological process occurs. Infants are placed on a phe-free diet because they have PKU, not to prevent their contracting PKU.¹⁴

Turning from diseases as processes, I would now like to consider whether classical PKU is a particular natural kind of bodily state. Boorse (1977, 555; cf. 558, 562), for example, says that "a disease is a type of internal state which impairs health, i.e., reduces one or more functional abilities below typical efficiency." The disease is not the functional impairment itself, but rather the state responsible for the impairment. Different tokens belong to the same disease category by virtue of involving the same natural kind of state.¹⁵

But some diseases are difficult to identify with particular bodily states. For example, an elevated level of phe (or its metabolic derivatives) in bodily fluids and tissues is not necessary for classical PKU, since as we just saw, phenylketonurics who eat no phe avoid an elevated level. Moreover, an elevated phe level is not sufficient for classical PKU; there are other hyperphenylalanemias (HPA's) besides classical PKU. (They are termed "non-classical PKU's.")

Classical PKU involves deficiency in the liver enzyme phenylalanine hydroxylase¹⁶ (pheOH), which catalyzes the first step in the catabolism of phe: its conversion to tyrosine. Another HPA involves deficiency in the other cofactor required by the same reaction: L-erythro-5,6,7,8-tetrahydrobiopterin (BH₄). Still other HPA's involve deficiencies in various enzymes that regenerate BH₄ from what it becomes as a result of helping to hydroxylate phe. Unlike classical PKU, symptoms of these other HPA's are not avoided by eliminating dietary phe, since BH₄ is also needed for tyrosine and tryptophan catabolism and to make various neurotransmitters.

Since having classical PKU is not having high phe levels, what other state might it be? Classical PKU cannot be the state of synthesizing too little pheOH, since some phenylketonurics produce plenty of pheOH, but the amino acid sequence of their pheOH renders it unstable, so that at any moment, they have too little pheOH. Classical PKU cannot be the state of having too little pheOH, since some phenylketonurics have plenty of pheOH, but the amino-acid sequence of their pheOH renders it "inactive" (i.e., unable to catalyze the reaction at a sufficiently rapid rate).

Consider an amino-acid sequence for an active molecule of pheOH. Do you have classical PKU if and only if you lack pheOH with that particular amino-acid sequence? No: there are many amino-acid sequences that yield active pheOH. There is even greater diversity in the DNA base sequence coding for active pheOH. The enzyme contains over 450 amino acids, and over 500 mutant alleles have been found so far, many of which are not pathological ("silent polymorphisms").¹⁷

Is classical PKU the state of having insufficient pheOH with this amino-acid sequence or that one or that other one or . . . (listing all and only the active forms of pheOH)? (An analogous proposal could be made regarding the DNA base sequence of the pheOH gene.) Although this state may be coextensive with classical PKU, it is not a natural kind of bodily state. It is motley. These forms of pheOH are distinguished from others merely by being all and only the active forms. A pheOH molecule's being active is not a state; it is a disposition. We have thus arrived at the verge of interpreting classical PKU as an incapacity.

Before turning to that interpretation, here is a final problem with understanding a disease as a kind of state. If having a given disease were having some kind of gene (or protein), then having that gene (or protein) could not be a cause of that disease, on pain of the disease's causing itself. Yet we do refer to "the genetic diseases that result from variations in our genetic messages" (Watson 1990, 46; cf. Cranor 1994, 131), which would be incorrect if having those diseases were nothing but those variations. Likewise, suppose that having emphysema were just being in a certain state: having broken or weakened walls between the alveoli in the lung. Then the fact that Jones has emphysema could not explain or be explained by Jones's having broken or weakened alveolar walls, since that would amount to a state's explaining itself.

VI. DISEASES AS INCAPACITIES

Classical PKU is best understood as an incapacity. This incapacity may be present even when there is no opportunity to catalyze phe (and consequently no PKU symptoms) because of a phe-free diet. Classical PKU is not the incapacity to catabolize phe since all other HPA's also involve this incapacity. Likewise, classical PKU is not the incapacity to hydroxylate phe since BH_4 -deficiency also involves this incapacity. Rather, classical PKU is the incapacity to make enough active pheOH.¹⁸

How much is "enough"? There is no sharp distinction; there are milder and more severe cases of classical PKU.¹⁹ What makes some amount of pheOH activity qualify as "enough"? (Why is a phenylketonuric on a phe-free diet still not making "enough" active pheOH?) A disease ascription takes place against a (generally tacit) understanding of the sorts of larger capacities that are part of good health. Just as there is a tacit understanding of what a "normal" diet is, roughly speaking, so there is a tacit understanding that the capacity to eat such a diet (without certain effects) is part of being in good health. This capacity is compromised by the incapacity to make enough active pheOH.²⁰

The incapacity to make enough active pheOH is a common cause of classical PKU's various symptoms (though, of course, it is not the only common cause; eating phe is another). Furthermore, a given pair of alleles of the pheOH gene is a cause of classical PKU; Jones's genotype explains why Jones lacks the capacity to

make enough active pheOH. Thus, the interpretation of classical PKU as an incapacity avoids the difficulties encountered by other proposals in accounting for the disease's explanatory role.

Objection: Consider an individual who has the incapacity that I have identified as essential to classical PKU. Suppose she has a rare gene coding for a protein that allows her to avoid the unfortunate symptoms of PKU, such as a protein allowing her to catabolize large quantities of phe through some other metabolic pathway or to transport other amino acids across the blood/brain barrier without interference from accumulated uncatabolized phe. On my proposal, this individual has classical PKU even though she would derive no ill effects from eating an ordinary, phe-full diet.

Response: That result is correct and accords with medical practice. Such individuals have been found and are described as having classical PKU (Trefz et al. 2000; NIH Consensus Development Panel 2001, 973).²¹ Indeed, a disease can be asymptomatic for many reasons—not just because something else (perhaps even a second disease) happens to compensate for the incapacity, but also because the incapacity has not lasted long enough to cause the loss of any larger-scale capacity. In either case, the disease is present because the smaller-scale incapacity essential to it is present. Contrast Typhoid Mary, who was “the bearer and distributor [*sic*] of the infecting agent of typhoid fever without developing the disease” (Reed et al. 1900, 202) because she was capable of easily keeping the typhoid microbe population in her body small enough. Someone else who is likewise asymptomatic and has a small typhoid microbe population in her body just as Mary does, but (unlike Mary) is incapable of easily keeping that population small, has (an early stage of) typhoid fever. She has the incapacity distinguishing that disease.

Infectious diseases like typhoid fever are paradigmatic disease categories. The account of diseases as natural kinds of incapacities identifies such a disease with the host's incapacity to easily keep in check the given microbe's population within the host. (“Easily” admits of degrees and should not be understood to permit certain outside aids, such as medication—no matter how easily it can be taken.) For some kinds of microbes, the host ordinarily harbors a significant (though stable) population, but other factors (such as immunosuppression or a change in the population of other kinds of microbes within the host) can turn the population from colonizing to infectious. For other kinds of microbes, the host ordinarily loses the capacity to keep the population in check when even a small number of microbes of this kind enter the host; even a small population is out of control. In that case, the host already has one incapacity even before any such microbe has entered her body: the host is incapable of preventing the uncontrolled growth of the microbe's population *if a small number of these microbes enter her body*. But before any such microbes have entered, the host possesses this incapacity without possessing the disease. (The same point applies to microbes of the former kind: even before the host is immunosuppressed or otherwise afflicted with the disease, she is incapable of preventing the uncontrolled growth of the microbe's population *while she is immunosuppressed*.)

Let's call this incapacity the host's "standing incapacity" in order to distinguish it from the incapacity that constitutes the disease. The host is afflicted with the disease only when she is incapable of controlling the microbe's current population in her body. Just as by moistening a match, we cause it to lose its capacity to light when struck, so by introducing a very small population of the microbe within the host, we may cause the host to lose the capacity to control easily that microbe's population inside her body.²² The host's standing incapacity entails that the host would acquire the disease under certain circumstances, and the standing incapacity may (together with the presence of those circumstances) explain why the host contracted the disease on some occasion. (For example, Roosevelt's having no resistance to and being exposed to the polio virus explains his contracting poliomyelitis.) But this explanation does not involve the disease's explaining itself, since the standing incapacity is not the incapacity constituting the disease.

If a disease is an incapacity, then one disease is distinguished from another by involving a different incapacity, and a disease (the incapacity to X) is a natural kind insofar as X is not an arbitrary, gerrymandered category. For example, the incapacity to make enough active pheOH on Wednesdays is not a disease, and neither is the incapacity to make either enough active pheOH or enough active BH₄. Once again, there will be intermediate cases and the proposal must match our intuitions regarding which cases are more and less paradigmatic. The common cold, for example, involves infection with any of many different microbes. The incapacity to repel easily an invading rhinovirus of a particular species is a specific disease partly because the species is a natural kind.²³ However, the common cold is also a disease, though a less paradigmatic one, because the rhinoviruses as a whole form a fairly natural grouping. The same applies to malaria, which can be caused by several species of *Plasmodium* bacteria.²⁴

The account of diseases as natural kinds of incapacities thus allows certain incapacities to be more or less "borderline cases" of disease categories. It also explains what was right about "same cause = same disease": the relevant "cause" is not an efficient cause, but rather the incapacity to X. That the same incapacity can have quite different efficient causes in different patients is no obstacle to its qualifying as a specific disease. Furthermore, since injuries, anatomical variants, burns, deformities, swelling, and anatomical lesions are states rather than incapacities, they are not diseases.

However, as we saw earlier, not all incapacities are diseases: blindness, color blindness (Campbell et al. 1979), hemiplegia (paralysis of the arm and leg on the same side), and various other disabilities and impairments are definitely not diseases (though poliomyelitis, which can produce paralysis, definitely is). How can this be accounted for on the view that diseases are incapacities?

Cummins (1975) has identified an important variety of biological (and not just biological) explanation: explaining how a system has the capacity to X by decomposing ("analyzing") that capacity into various subcapacities possessed by the system or its components. Cummins calls this a "function-analytic explanation" and says,

The explanatory interest of [a function-analytic] account is roughly proportional to (i) the extent to which the analyzing capacities are less sophisticated than the analyzed capacities, (ii) the extent to which the analyzing capacities are different in type from the analyzed capacities, and (iii) the relative sophistication of the program appealed to, i.e., the relative complexity of the organization of component parts/processes which is attributed to the system. (1975, 764)

For example, an explanation of the heart's capacity to go "lub dub" in terms of its capacity to go "lub" and its capacity to go "dub" would lack any interest, whereas an explanation in terms of the atrial-ventricular node's capacity to conduct signals (and other similar capacities) would be more interesting.²⁵

I take a similar view of what makes an explanation supplied by an incapacity interesting. A disease is an incapacity that is explanatory. Insofar as the capacity to X can figure as a component in an interesting function-analytic explanation of the capacity to Y, the incapacity to X can figure in an interesting explanation of the incapacity to Y, and so tends to better qualify as a disease. Therefore, although Jones's incapacity to walk might be explained by Jones's incapacity to move his right leg, this explanation is far from interesting (and so paralysis of the right leg is not a disease) because the capacity to walk is not interestingly decomposed into the capacity to move the right leg and other such capacities. (The incapacity produced by a broken leg is likewise not a disease.) In contrast, the incapacity to eat ordinary bread without various PKU symptoms is interestingly explained by the incapacity to synthesize enough active pheOH because the capacity to eat ordinary bread without various PKU symptoms is interestingly decomposed into the capacity to synthesize enough active pheOH and other such capacities.²⁶

The capacity to release the neurotransmitters GABA (gamma-aminobutyric acid) and glycine figures in a good function-analytic explanation of ordinary muscle control. Therefore, the incapacity to release these neurotransmitters (which results from, e.g., the tetanus bacterium's releasing tetanospasmin, which binds to the gangliosides at the ends of neurons) figures in a good explanation of the loss of ordinary muscle control. Tetanus is therefore eligible to be a disease (though, as I mentioned earlier, tetanus does not essentially require that the incapacity to release these neurotransmitters be caused by the tetanus bacterium).

In contrast, injury from an attacking lion (or an automobile accident) is not a disease (since it is a state, not an incapacity), and the incapacity to repel easily an attacking lion is not a disease, since the corresponding capacity does not figure in an interesting function-analytic explanation. Admittedly, Jones's capacity to repel easily an attacking lion might help to explain Jones's having been able to avoid serious injury during her recent safari. But this is not an interesting function-analytic explanation since the capacity to repel an attacking lion is not obviously much simpler than and different in kind from the capacity to avoid serious injury during a safari.

Here is a different sort of example. Blindness is an incapacity, and "Because Jones is blind" would in many contexts adequately answer why-questions such as

"Why can't Jones drive?" Yet blindness is not a disease because the capacity to see is not a component in an interesting decomposition of (say) the capacity to drive. Recall point (iii) in Cummins's remark. Seeing does not occupy some subtle niche in a complex organizational scheme for driving; being able to see stands in no interesting relations to other capacities that together with it comprise an intricate network of interrelated capacities that amount to being able to drive. Rather, being able to see is simply a prerequisite for many of the capacities into which the capacity to drive might interestingly be decomposed. It is like being able to fit into a car. (I take a similar view of colorblindness,²⁷ shortsightedness, and suffocation.)²⁸

Starvation and malnutrition are not diseases because, although they lead to various incapacities, they are not incapacities themselves. Being malnourished is a state. On the other hand, being unable to absorb a certain specific nutrient can be a disease, even though one might call it "being starved" of that nutrient.

Lead poisoning is an intermediate case. On the one hand, having lead inside of your body is a state, and exposure to lead seems no more like a disease than does exposure to 600° temperatures. The capacity to withstand the heat of your current environment typically does not figure in any interesting function-analytic explanations, and the capacity to withstand the amount of lead in your current environment might well seem similar. However, the biochemical incapacities produced by lead poisoning are quite specific (since lead binds with enzymes that use zinc, iron, and calcium as cofactors, rendering them inactive) and the corresponding capacities figure in interesting function-analytic explanations. Nevertheless, part of what distinguishes lead poisoning, especially in the minds of those less familiar with these incapacities, is that it requires lead; if it was discovered that the same incapacities could also be produced by exposure to osmium, many of us would not say that a new cause of lead poisoning had been discovered. But we would if we had the biochemical incapacities primarily in mind. This result accords with the survey findings of Campbell et al. (1979): lead poisoning was regarded as a disease by almost 70 percent of general practitioners and nearly 90 percent of medical academics, but by only 30 percent each of nonmedical academics and secondary-school students. (Carbon monoxide poisoning was similar.)

The survey produced a similar result for duodenal ulcer. Although an ulcer is a state (a hole in the lining of the duodenum), physicians discuss "peptic ulcer disease," which I take to be a posited incapacity leading to ulcer formation. At the time of the survey by Campbell et al., peptic ulcer disease was widely believed to be something like the incapacity to keep stomach acid secretion below a high level. Today it is believed to have more to do with the incapacity to resist easily the invasion of certain bacteria. In any case, physicians believed there to be a common (though not fully understood) incapacity responsible for ulcer formation.

Cholelithiasis (the presence of gallstones) is a different sort of intermediate case, according to the survey by Campbell et al.: all four groups (general practitioners, medical academics, nonmedical academics, and secondary-school students) agreed in placing it far from the most canonical diseases but as much more disease-

like than starvation, color blindness, and fractured skull. Whereas having gallstones is a state, not an incapacity, it is closely associated with an incapacity (being unable to pass bile through the common bile duct) where the corresponding capacity figures in interesting function-analytic explanations. However, in contrast to ulcers, gallstones were known to be caused by many different diseases. (Impaired gallbladder motility tends to produce cholesterol stones, while diseases involving abnormal hemoglobin metabolism or increased erythrocyte destruction tend to produce pigment stones). No single disease was posited as resulting in gallstones.

When the capacity to X figures as a component in an interesting function-analytic explanation of the capacity to Y, the latter capacity may itself figure in interesting function-analytic explanations, and so both the incapacity to X and the incapacity to Y may constitute diseases, the former constituting a variety of the latter. For instance, classical PKU produces an incapacity to metabolize phe, which in turn produces hyperphenylalanemia (HPA), an incapacity to keep blood levels of phe (and its metabolites) low enough. HPA explains further incapacities and symptoms. For example, high phe blood levels yield mental deficits because (it is believed) blood phe outcompetes other large neutral amino acids for transport across the blood/brain barrier, depriving the brain of various essential amino acids. HPA is eligible to explain only because it is a natural kind of incapacity, and it is a specific disease only because it actually turns out to have explanatory significance. Compare HPA to hyperphenylalaninuria (the *symptom* of having high phe levels in urine). Physicians do not refer to "the hyperphenylalaninurias" in the way they refer to "the hyperphenylalanemias" because the incapacity to keep urinary phe levels low enough, although a natural kind of incapacity, is not a disease because (unlike HPA) it does not explain other incapacities. There is nothing downstream (as it were) from hyperphenylalaninuria. Rather, hyperphenylalaninuria is merely a side effect of HPA.

In other cases, what once seemed to be a single disease was revealed not to be a well-defined disease at all, but to encompass many specific diseases. Let's look at an example. Myocardial infarction ("heart attack") is an event: the death of heart muscle from sudden blockage of a coronary artery. Coronary atherosclerosis is a process: the gradual narrowing of a coronary artery's inner channel and hardening of the arterial walls by deposition of cholesterol plaques. It can begin in teenage years. As we saw, this process cannot explain a coronary artery's current narrow state because that state is a part of the sequence that constitutes the process. However, atherosclerosis of one artery is statistically correlated with atherosclerosis of other arteries. Apparently, there exists a systemic tendency, which had been believed to result from a single disease: coronary artery disease.²⁹ However, this "disease" was found to take many forms, leading to no common incapacity that could be coronary artery disease (unlike the many forms of HPA). One form it was found to take is familial hypercholesterolemia, caused by a mutation of a gene on chromosome 19. This gene codes for a receptor on the surface of cells that is involved in the uptake of low-density lipoprotein-cholesterol (LDL) particles. The incapacity to take up LDL

particles results in an incapacity to keep plasma cholesterol levels low enough, contributing to atherosclerosis. Other cases of "coronary artery disease" involve none of these incapacities. Discoveries like this revealed "coronary artery disease" not to be a disease, whereas familial hypercholesterolemia and other heritable disorders of lipid homeostasis are specific diseases. "One had now to believe that coronary artery disease was many diseases, genetic predisposition playing a different role in the different forms" (Scriver and Childs 1989, 194; cf. Brown and Goldstein 1986).

The HPA's are distinct diseases each causing the same incapacity, which itself is a distinct disease (HPA), whereas apparently the forms of "coronary artery disease" yield no common incapacity, and so "coronary artery disease" is not a single disease. Some examples fall between these two. Cancer, for instance, is the incapacity to regulate the growth and reproduction of certain cells. But this incapacity, though unifying all cancer, is rather vague because the proper regulation of cell growth and reproduction is achieved by a combination of many separate capacities, each of which must be disabled in some (perhaps independent) way for a tumor to form and to metastasize. For example, cells of a given type are usually stimulated to grow by signals from their neighbors (paracrine signals) or by systemic (endocrine) signals, involving some exogenously produced signaling molecule binding to a membrane receptor. A cancer cell is unable to have its growth regulated in this way because it either synthesizes its own growth factor, or stimulates surrounding cells to produce additional growth signals, or has membrane receptors that respond to levels of growth factor ordinarily too low to trigger growth. In addition, a cancer cell must be insensitive to signals that ordinarily inhibit growth, resistant to programmed cell death (apoptosis), lose the ordinary limitation on the number of cell divisions that a lineage can undergo, and so forth. Each of these incapacities is necessary for tumorigenesis (Hanahan and Weinberg 2000). Although they might all be lumped together as constituting a single incapacity (to regulate cell growth and reproduction), this incapacity is not especially unitary. All cancer involves the same incapacity, but this incapacity itself turns out to be something of a hodgepodge. It might better be described as a conjunction of various incapacities (such as the incapacity to respond to variations in exogenous growth signals).

VII. THE END OF DISEASES

Diseases have long been central to medicine because the goals of medicine³⁰ have heretofore been best advanced by taking diseases to be natural kinds. For example, the best strategy for predicting what would happen if Jones were subjected to a given therapy has been to examine the past outcomes of so treating other patients similar to Jones, and an important respect of similarity has been their having the same disease as Jones. However, this role and others characteristic of natural kinds will in coming years be played in medicine less and less by diseases. Whereas med-

icine over the past few centuries has progressed partly by identifying and differentiating additional disease categories, genomic and proteomic medicine (and molecular medicine more generally) will instead lead to the end of diseases as useful medical categories. Let's see why this is so.

As we have seen, a disease is a natural kind of incapacity. But even when the incapacity is well defined at the molecular level, there will be heterogeneity in its molecular basis; it will be multiply realized. Medical explanations of a token illness's manifestations, predictions of its course, and choices among possible therapeutic strategies will increasingly be based not on the disease category to which the token belongs, but rather on the token's specific molecular subtype. A subtype will not be a natural kind of incapacity. Therefore, it will not be a distinct disease. Furthermore, many subtypes will contain only a single token illness. Predictions in medicine will be made not by drawing upon our past experience with other cases of the same subtype, but by inferences from chemical laws and the patient's biochemical state—that is, by modeling a given patient's (or cell's) "molecular signature," which includes its gene and protein activity patterns and the chemically specific environmental influences to which it is subject. Medical explanations will likewise appeal to chemical laws and initial conditions rather than to generalizations (or even probabilistic or *ceteris-paribus* laws) covering all patients with a given disease. Clinical proteomics and pharmacogenomics combined with computationally sophisticated simulation techniques have initiated a revolution in patient care often called "individual medicine" (a.k.a. "personalized molecular medicine," "patient-tailored therapeutics," and "molecular diagnostics"):

In the next decade, patients are likely to have their individual genomes and transcriptomes stored as part of their medical records. Fine-tuning treatment on a case-by-case basis will become the norm. (Williams 2006, 53; cf. Cortese 2007; Liotta et al. 2001)

Diseases will remain natural kinds, capable of grounding explanations and predictions, but medicine will no longer call upon them to serve as natural kinds.

Consider classical PKU. The Online Mendelian Inheritance in Man (OMIM) database currently lists over 65 alleles in the pheOH gene (on chromosome 12) that produce classical PKU. Each of these alleles (whether involving a missense or nonsense mutation, a single base-pair frame shift, or a larger deletion or insertion) creates the same incapacity: to make enough active pheOH. This incapacity can be created in different ways (e.g., by making pheOH that fails to bind phe, or making no pheOH at all, or making unstable pheOH), possibly leading to subtly different clinical manifestations. However, the different PKU allelic variants cannot all be distinguished as causing different incapacities—that is, separate diseases. The opportunity for biochemical and clinical heterogeneity among phenylketonurics is increased further by the fact that phenylketonurics are usually heterozygotes and (as we saw) may also differ in their capacities to exploit other metabolic pathways for catabolizing phe.

None of these facts undermines classical PKU's status as a natural kind of incapacity figuring in interesting function-analytic explanations of other incapacities. But these facts entail that as medicine increasingly tailors its explanations, predictions, and therapies to each patient's specific PKU allelic variant—or, rather, to each patient's entire genome—classical PKU can no longer serve as a medical natural kind. Some genomes will require phe-free diets, whereas others will tolerate somewhat greater dietary phe levels. Any therapy that aims to “fix” a PKU allele, to affect the regulation of its expression, to alter its product so as to augment that protein's activity, or to exploit other genes to compensate for pheOH deficiency will have to be targeted to a particular genome.

Analogous considerations apply to infectious diseases. Immunizations and therapies are now targeted not to particular diseases, but to particular microbial strains and serotypes. For instance, intensive research is currently directed at the strains of avian flu virus similar to the strain responsible for the 1918 pandemic. Although bacterial pneumonia, for example, could be subdivided into hundreds of different diseases, each involving a different strain of *Streptococcus pneumoniae*, medicine will not be using these as natural kinds. Rather, physicians will “soon” design individualized therapies from “first principles”: by sequencing the genome of the strain infecting the patient, ascertaining the patient's immunological state (reflecting her genotype, current gene-expression profile, and personal history), and identifying the other genetic and environmental components of her unique individual susceptibility to infectious diseases and to adverse reactions from medication—“all this in 10 minutes using easy, inexpensive, office-based tests” (Hall 2003, 12).³¹ Accordingly, there will be no need to try to predict a given therapy's effectiveness for a given patient by induction from that therapy's past results for similar serotypes or strains. It will not be medically relevant to ask (e.g.) whether the flu now common in Romania is a different disease from the flu now common in Southeast Asia, since scientists will not be predicting a given treatment's effectiveness for one by inferring from its effectiveness for the other—i.e., by projecting across a medical natural kind. Pharmaceutical companies will attempt to develop novel vaccines or therapies only given precise genomic information regarding the intended infectious agent and infected host.

A patient's cancer will likewise be understood through genomic sequencing and gene expression profiles of tumor cells. DNA microarray studies of breast, lung, and liver cancers along with diffuse large B-cell lymphomas have already revealed that each individual tumor is quite dissimilar in its gene expression from other tumors, even those of the same organ in the same patient (Perou et al. 2000; Chung et al. 2002). Gene expression “profiling” creates a tumor “portrait” that (it is widely believed) will ultimately ground individualized therapies as well as scientific explanations in terms of the particular sequence of chemical events responsible for that particular tumor's development. When whole-genome sequencing of individual patients becomes feasible clinically, a tumor's individuality will be crucial to determining the optimal therapeutic regimen.

Similar considerations apply to diseases of the heart. Dilated cardiomyopathy (DC—the most common form of cardiomyopathy, a group of diseases affecting heart muscle) has so far been the main focus of proteomic research in cardiology. These studies have revealed some 100 cardiac proteins that have significant abnormalities in various DC patients (Banks, Dunn, et al. 2000, 1754). Some of these proteins are cytoskeletal and myofibrillar, others are associated with mitochondria and energy production, and still others are associated with stress responses. Of course, DC patients will also vary substantially in the genes responsible for the toxicity of various therapeutic interventions. Accordingly, therapy will increasingly be designed to target an individual patient's distinctive biochemical pathways.

Thus, rather than molecular medicine supplying merely “a new taxonomy of disease” by refining and narrowing disease categories (as predicted by Bell 2003, 215), I contend that molecular medicine is well on its way to rendering diseases obsolete as medical natural kinds. Of course, people will still be afflicted with diseases and disease categories will remain natural kinds and may still have a host of medical applications (e.g., in facilitating communication, organizing subdisciplines, and processing insurance claims). But “predicting which patient will respond to what treatment and assessing prognosis [and, I would add, explaining phenomena—ML] are the very reasons for assigning patients to diagnostic subtypes” (Akiskal 1987, 63). The rationale for doing so will have disappeared in an age when molecularly targeted therapies, gene expression profiling, and whole-genome sequencing are routine. Diseases will then have ceased to be medical natural kinds.

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NOTES

1. According to Aronowitz, the fact that residual diagnostic categories typically go unrecognized as specific diseases is evidence that “social influences have largely determined which symptom clusters have become diseases” (2001, 803). I disagree: inference to the best explanation is unlikely to support regarding a residual category as a single disease, since a diagnostic wastebasket tends to be heterogeneous. Sometimes, however, the evidence justifies positing a single disease as embracing all cases in a ragbag category. Bodenreider et al. (2004) mention non-Hodgkin lymphoma and non-insulin dependent diabetes mellitus as examples.
2. Margalit (1979, 37) disagrees; he says that since a disease is a deviation from normal functioning and a disease's symptoms constitute a deviation from normal functioning “just like its other aspects,” they “constitute the disease” along with those other aspects. He does not discuss a disease's explanatory role. Various jokes (e.g., “A dermatologist is a doctor who tells you in Latin what you have just told him in English”) exploit the fact that a disease is supposed to be sufficiently distinct from its clinical manifestations to explain them.

3. Indeed, Kendell (1982, 1338) says that when the neurophysiological basis for a psychosis is found, "the defining characteristic of the disease will change," since it was formerly defined "operationally." Cunningham (1992) agrees, holding that plague was "transformed from a disease whose identity was symptom-based into one whose identity was cause-based" (224); on this view, the discovery of the plague bacillus did not reveal the cause of the same disease that had long been the subject of attention. This seems mistaken; as Kendell himself emphasizes, the operational diagnostic criteria for a psychiatric illness always aimed to capture something neurophysiological. Moreover, if the *DSM* gave definitions rather than merely diagnostic criteria, then whether a patient has a given disease at a given moment would in some cases depend on whether her symptoms last longer than a certain period encompassing that moment. For example, *DSM-IV-TR* (2000) requires that a "manic episode" persist for at least one week. If this requirement is part of the definition of "manic episode" (rather than merely a diagnostic criterion), then a patient who died from a traffic accident before the requisite week had elapsed would not have had a manic episode despite being (until the accident) similar in all relevant respects to another patient who lived long enough to fall under the criterion.
4. "When we find that a condition such as retinitis pigmentosa sometimes descends in one way and sometimes in another, we may perhaps expect that a fuller knowledge of the facts would show that more than one pathological state may be included under the same name" (Bateson 1909, 234).
5. The *ceteris-paribus* proviso is necessary because other information about differences between the patients can eliminate this confirmatory relevance (Bartlett 1844, 122, 129). Notice, however, that even important differences between the patients can fail to eliminate the relevance—as when therapeutic trials on members of one species afflicted with a disease serve as evidence regarding how members of another species having the same disease would respond.
6. Perhaps essential hypertension is merely a residual category or a sign (Jenning and Netsky 1991), not a specific disease. But the same argument (from the continuity between having and not having a given disease) could be made regarding better candidates for diseases than essential hypertension.
7. Certain "transient mental illnesses" seem to require a certain cultural context and so, it might be argued, are not natural kinds. (See Hacking 1998 for discussion.) However, even if this argument succeeds, it fails to generalize to the putative disease categories on which I shall focus.
8. Presumably, this view motivates Boorse (1977), Brock (2001, 76), and Cooper (2002) to take pathological conditions generally (rather than diseases) as their target. Boorse (1977, 551) writes, "our analysis of disease will include conditions like fever, diarrhea, dyspnea, hypoglycemia, and so on, which are not considered individual diseases by medical sources. In this respect alone we make no attempt to be faithful to the customary extension of 'disease.'" Accordingly, Boorse also deems deafness and limb paralysis to be diseases (550).
9. Because this distinction is not always respected, a good deal that has been written concerning disease individuation by causes is difficult for me to understand. For instance, Goosens (1977, 135) writes, "Nor . . . would it be correct to regard jaundice as its symptoms." I agree—but surely no one ever considered "Jaundice is its symptoms—that is, its effects" to be a possibility! Likewise, Goosens writes, "It might be suggested that tuberculosis is not just caused by an organism, but is the presence of an organism" (136). But if tuberculosis is the organism's presence, then it cannot be caused by the organism's presence.
10. Whitbeck (1977, 635) says that "it is likely that aspects of the present model [of disease individuation] . . . will not survive into the future" because some diseases, such as cancer, will be discovered to have many causes but no factor that is *the* cause. I believe that Whitbeck's account of the "present model" is inadequate even in simpler cases.
11. An objection to diseases as processes: How are the limits of the disease process fixed? Seeking medical attention, for example, is not part of a disease process, yet like later stages in the disease process, it is caused by earlier stages.
12. Austin (1961, 77) says that having mumps is "a whole pattern of events, including occasion, symptoms, feeling and manifestation, and possibly other factors besides. It is . . . silly . . . to attempt to fine down 'the disease' to some one chosen item ('the functional disorder')." But how can the mumps explain various clinical manifestations if those symptoms are part of the disease?
13. Of course, future medical research could reveal that pheOH deficiency has certain unhealthful

consequences even on a phe-free diet. However, for the sake of argument, I shall take current medical opinion to be correct.

14. Here I disagree with Brock (2001, 78): "All disease occurs in organisms with a particular genome existing in a particular environment, typically from an interaction of genetic and environmental conditions. Phenylketonuria (PKU) occurs when a person without a gene that produces an enzyme needed to metabolize phenylalanine eats a normal diet that is high in phenylalanine." Likewise, Craner (1994, 137): "PKU (an accumulation of phenylalanine that results in mental retardation) ..." Medical literature is also occasionally sloppy. Donlon et al. (2001, 1667): PKU "is an autosomal recessive (Mendelian) trait (OMIM 261600) with a multifactorial cause: mutation in the human phenylalanine hydroxylase (symbol *PAH*) gene and exposure to dietary phenylalanine are both necessary and sufficient conditions." If the trait is genuinely autosomal recessive, then it cannot depend on dietary phe. Most medical literature correctly describes PKU as an inborn error of metabolism and notes that a phe-free diet prevents the disease manifestations, not the disease. Boorse (1977, 561, 562) also gets it right.

Cuiver and Gert (1982, 72) say that a condition is a "malady" only if it causes or increases the risk of suffering an evil and "this evil (or increased risk thereof) one is suffering is not in continuing dependence upon causes clearly distinct from oneself. . . . Thus, a wrestler's hammerlock upon a person . . . is not a malady." Is classical PKU? The mental deficit it produces given a normal diet is not in continuing dependence on external causes; once produced, the deficit is irreversible. However, consider a phenylketonuric at birth. If her deficiency in a certain enzyme increases her risk of suffering an evil, then that risk depends on the risk of phe's being present in her diet; put her on a phe-free diet and the risk disappears. So isn't the risk in continuous dependence on causes distinct from herself? Gert (personal communication) replies that loss of freedom to eat a normal diet is an evil that is not in continuing dependence upon external causes.

15. Most of the literature regarding Boorse's proposal concerns Boorse's statistical conception of health. Boorse's interpretation of diseases as kinds of internal states has gone relatively neglected. Plainly, injuries and wounds are also states, but Boorse explicitly does not aim to distinguish diseases from other pathological conditions (see note 8).
16. A.k.a. phenylalanine dehydrogenase, phenylalanine 4-monooxygenase.
17. The Phenylalanine Hydroxylase Locus Knowledgebase (www.pahdb.mcgill.ca) lists the known mutant alleles.
18. That is why classical PKU is now sometimes identified (e.g., by Donlon et al. 2001) as "pheOH deficiency." Of course, a disease can be discovered long before the precise incapacity individuating it is identified. By an "incapacity," I mean nothing more than the lack of a certain capacity, and a capacity is simply a disposition (i.e., a power). A fragile vase has the capacity to break and an incapacity to speak, for example.
19. Indeed, there is also no sharp distinction between "active" and "inactive" pheOH, since there is a smooth continuum of rates at which various amino-acid sequences of pheOH catalyze hydroxylation. Classical PKU might better be described as the incapacity to make pheOH with enough activity. Both "incapacity" and "activity" refer to dispositions.
20. I shall consider no further (except in the next note) what, if anything, makes a tacit understanding of health accurate—the first of the questions I enumerated in section 3. My point is merely that some such understanding is invoked in disease ascription. That the capacity compromised by classical PKU is part of being in good health plays no role in scientific reasoning concerning the causes, effects, treatment, and prevention of classical PKU, though it may motivate that research.
21. This is a good example to offer in response to Thagard's view:

At the level of organisms, the notion of function can indeed take on a normative dimension But at the cellular level, normal functioning can be characterized in purely biological terms by answering the question: what are the biochemical pathways that universally operate in particular types of human cells to enable them to perform energy acquisition, mitosis, motion, adhesion, signaling, and apoptosis? Once these pathways are identified, abnormality can be recognized as a biological notion Hence when the

explanation and treatment of disease operates at the level of biochemical pathways, it provides support for the naturalistic, nonnormative conception of disease. However, not all medicine operates at the pathway level, and I leave open the possibility that a more general conception of disease may need to take into account valuations as well as biological explanations. (Thagard 2003, 250)

I disagree. Human beings differ even in the biochemical pathways they use in energy acquisition and so forth, as illustrated by the diversity in the pathways by which they catabolize phe.

According to Thagard (2003), "malfunctional explanations" fit the following schema (with bracketed terms subject to replacement):

Why does a [system] fail to [function] normally?

Because normal [function] in the [system] is produced by a [mechanism] with a set of [entities] and [activities].

The [mechanism] has [defects] in some [entities] and [activities].

So the [system] cannot [function] normally.

However, the conclusion ("So ...") follows only if the system can carry out the function (e.g., catabolizing phe) normally only by the designated mechanism. However, a defect in the mechanism normally used to catabolize phe does not invariably result in the system's failure to catabolize phe. Unless "normal function" in this case is defined not merely as catabolizing phe, but as doing so through a particular mechanism, the system can function normally even if the designated mechanism has defects. (Indeed, one defect can compensate for another.)

22. Admittedly, it sounds somewhat strained to say that a host loses the capacity to keep in check the microbe population she harbors merely by such a nonzero population existing in the first place. The host might seem to have no capacity at all to control this microbe's population, and so no capacity to lose. However, I don't intend the population's being "kept in check" to suggest that the host must be doing something to discourage its growth. Whether a host harbors no microbes or a stable nonzero population, she may be capable of "keeping in check" the population she harbors—just as long as no microbes enter. The host may lose this capacity as a result of some microbes entering.
23. Of course, whether a biological species is a natural kind has been hotly debated. Boyd (1999) offers an account of species as natural kinds that recognizes synchronic and diachronic variation among conspecifics.
24. It is commonly said that more children die of malaria each year than any other single disease.
25. Cummins's account of the explanatory value in decomposing one capacity into an organized array of various subcapacities is only as precise as the notions of subcapacities being simpler than the original capacity, different in kind from it, and elaborately organized. To my knowledge, no philosophical account of function-analytic explanation has articulated these desiderata more fully than Cummins does, and I cannot do so. Nevertheless, such criteria are commonly invoked—as when Dennett (1978: 80) says that psychological explanations of mental capacities analyze one homunculus into *less clever* homunculi. It seems to me that we often need no further articulation of Cummins's criteria in order to recognize easily that one decomposition better satisfies them than another. For example, Amundson and Lauder (1994, 450–51) use Cummins's criteria to compare the explanatory value of two decompositions of a jaw's crushing capacity. An explanation that attributes the jaw's capacity to a particular muscle's capacity to crush the upper and lower jawbones together while they remain rigid is a "functional analysis of very low value" because the organization of the subcapacities is "almost degeneratively simple, and the force of the muscle hardly simpler or different in kind from the crushing capacity of the jaw." In contrast, a decomposition of the jaw's crushing capacity in terms of the capacities of various weaker muscles acting in a coordinated fashion to produce a rolling and grinding cycle scores well by Cummins's criteria. One muscle might move a bone in only one dimension, so its capacity is simpler than and different in kind from the jaw's three-dimensional motion, and the subcapacities' organization is complex.

26. Different species may use different enzymes to catabolize phe. Because many human beings use pheOH, a given human being's incapacity to make enough active pheOH can help to explain her incapacity to catabolize phe. Hence, classical PKU (pheOH deficiency) is a disease category for human beings; as we saw, it can afflict even a human being who has a rare gene allowing her to catabolize phe without making pheOH. Suppose there is a species no member of which synthesizes pheOH, though most can still catabolize phe. Suppose, however, that a given member of that species is incapable of catabolizing phe. Her incapacity to make pheOH would not help to explain this incapacity, since the capacity to make pheOH does not help to explain the capacity of any member of her species to catabolize phe. Since a disease must figure in such explanations, pheOH deficiency is not a disease to which members of this species are susceptible. (Once again, there will be intermediate cases.)
27. However, for some specific biochemical capacity that figures in a function-analytic explanation of the capacity to distinguish red from green, the corresponding incapacity would qualify as a disease. Accordingly, when red-green colorblindness is described as a hereditary, sex-linked trait, it is often characterized as a disease (e.g., by Bateson 1909).
28. Congestive heart failure might well be an intermediate case—where the function-analytic explanation is somewhat interesting.
29. Sometimes "coronary artery disease" is used simply as a synonym for atherosclerosis.
30. These goals include promoting a patient's health, relieving her suffering, predicting her future health, and preventing sickness.
31. There may also be important non-genomic influences on a therapy's effects, including nutritional status, other drugs being administered, and gut microbiota.

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