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Defining Mental Disorder

Jerome Wakefield and His Critics

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17 Does Developmental Plasticity Pose a Challenge to the Harmful Dysfunction Analysis? Reply to Justin Garson

Jerome Wakefield

I have learned much from Justin Garson's insightful writings on the concepts of biological function and dysfunction (e.g., Garson 2016; Garson and Piccinini 2014), and I am grateful to him for his contribution to this volume that pushes his thinking about these concepts in some fresh directions. His paper usefully opens up the area of evolutionary developmental biology (known as "evo-devo") as an additional empirical domain in which to explore the validity of my harmful dysfunction analysis (HDA) of medical, including mental, disorder. The HDA claims that "disorder" refers to "harmful dysfunction," where dysfunction is the failure of some feature to perform a natural function for which it is biologically designed by evolutionary processes and harm is judged in accordance with social values (First and Wakefield 2010, 2013; Spitzer 1997, 1999; Wakefield 1992a, 1992b, 1993, 1995, 1997a, 1997b, 1997c, 1997d, 1998, 1999a, 1999b, 2000a, 2000b, 2001, 2006, 2007, 2009, 2011, 2014, 2016a, 2016b; Wakefield and First 2003, 2012). There has been only minimal attention to this area in the discussion of the HDA; one earlier interchange on this topic between Richters and Hinshaw (1999) and me (Wakefield 1999b) is reconsidered below, and the field has grown dramatically since then. A detailed analysis of evo-devo's implications for the HDA is long overdue, and I welcome Garson's invitation to return to this topic.

Many prominent critics of the HDA's approach to medical disorder agree with the idea that a disorder involves a dysfunction but disagree with the HDA's evolutionary interpretation of biological function and dysfunction (e.g., see the papers by Murphy and Lemoine in this volume and my replies). In contrast, Garson agrees with me that the concepts of biological function and dysfunction are best understood in evolutionary terms and instead targets the claim that medical disorder presupposes biological dysfunction.

Like some other prominent critics of the HDA (e.g., see my reply to Cooper in this volume), Garson holds that disorders can be naturally selected. He thinks this is possible because when naturally selected features that were adaptive in earlier species environments are maladaptively mismatched to today's altered environment, the mismatch between our biologically designed nature and the environment is or can be a disorder,

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contradicting the HDA's dysfunction requirement. No doubt many of our problems are due to such mismatches. However, as I shall show, this is not how our concept of disorder works and for good reason if the concept is to form the foundation of a viable medical discipline of psychiatry that resists antipsychiatric critiques.

Garson's "mismatch" argument is multilayered. He presents the evolved mismatch objection in three somewhat different forms. I will disentangle and somewhat reassemble the various arguments and build up to his main argument in steps parallel to his three arguments.

First Version: The Evolutionary Mismatch Objection

Garson initially argues for a standard form of the mismatch objection to the HDA that he christens the "evolved mismatch critique." In general, the recent evo-devo literature characterizes evolutionary mismatches as arising "upon exposure to an entirely novel environment, or to an environment that is beyond the evolved physiology and adaptive capacity of the individual" (Low and Gluckman 2016, 69). Moreover, such exposure occurs regularly because, as an authoritative book in the field explains, one of the "fundamental principles of evolutionary medicine" is that "humans now live in very different ways and in different environments from those where the majority of selective processes affecting the modern human phenotype operated. In this respect we are biologically 'mismatched' to many aspects of our current environment" (Gluckman et al. 2016, 162). These authors describe the general idea of evolutionary mismatches as follows:

> Environmental factors acting during the phase of developmental plasticity interact with genotypic variation to change the capacity of the organism to cope with its environment in later life. Because the postnatal environment can change dramatically, whereas the intrauterine environment is relatively constant over generations, it may well be that much of humankind is now living in an environment beyond that for which we evolved. (Gluckman and Hanson 2006b, 4)

> Evolutionary change is slow and our social and physical environments have changed very fast through the broader processes of cultural evolution. … The biological processes that determined our present structure and function largely evolved in very different environments from those we now inhabit. Thus, the most common way in which evolutionary pathways are associated with ill-health is through the consequential mismatch that can arise … when an individual lives in an environment which is evolutionarily novel or where the individual's evolved capacity to adapt is exceeded. One example … is obesity and its associated morbidities. Another example is the mismatch between the evolved reproductive decline in women, starting in the fourth decade of life, and the pattern of reproduction shaped by cultural evolution and widely practiced in modern societies, with later pregnancies and resulting demand for fertility services. Scurvy represents a historical example of mismatch. … During human evolution there

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> was continual access to fruit, and thus the mutation which led to our inability to synthesize vitamin C was "neutral" until exposed by an evolutionary novelty produced by cultural evolution (i.e., boats capable of long sea voyages during which a dietary source of vitamin C was absent). … Given that humans and our hominin ancestors survived as hunters and foragers for 99% of our existence, it can be argued that selection has driven our biology and metabolism to be better matched to the physical activity and diet that characterized the foraging way of life. From this perspective, the current global epidemic of metabolic disease can be understood, in part, as a result of a mismatch between our 'ancient' foraging-adapted genome and our rapidly changing modern diet and lifestyle. (Gluckman et al. 2016, 167, 210)

The objection to the HDA based on evolutionary mismatches is simply that problematic mismatches between an individual's naturally selected nature and environmental context are disorders, and thus dysfunction is not necessary for disorder. Garson notes that this is a "long-standing objection" that "Wakefield's opponents have repeatedly raised" and insists that "the evolved mismatch critique, when properly understood, undermines Wakefield's analysis." So, despite having addressed this objection before (Horwitz and Wakefield 2012; Wakefield 1999a, 2010), I consider the reasons for rejecting Garson's version of the mismatch thesis, which he poses as follows:

> What if some of our devastating psychiatric ailments, such as major depression, anxiety disorders, psychopathy, and so on, actually *benefited* our Pleistocene ancestors? What if, moreover, the *fact* that they benefited those ancestors partly explains why they are around today? Then, if we accept the selected effects theory of function, we would have to say that those disorders do not arise from "dysfunctions." They would be adaptations. Furthermore, if we accept the HD analysis, we would be forced to conclude that depression (say) is not actually a mental disorder. That strikes me as deeply counterintuitive. It seems to me that depression, particularly when severe enough to lead to hospitalization or suicide attempts, constitutes a paradigmatic mental disorder, regardless of how it happened to evolve.

Evolutionary mismatches are of course real and important to understand. However, Garson applies this perspective not as a scientific causal hypothesis to explain some problem but as a conceptual thesis about the meaning of "disorder." The best evidence against such a conceptual evolutionary mismatch thesis is our actual disorder judgments. Known mismatches between our evolved natures and current environmental conditions, no matter how problematic, are not intuitively considered disorders. For example, the evolved desire for sex with people other than one's partner is mismatched with our monogamous social mores, the evolved desire for high-fat and sweet foods is harmfully mismatched with the overabundance of such foods in our environment, and our evolved aggressive and fight-or-flight impulses when stressfully interacting with others are mismatched with our dense, high-interaction, and often frustrating social environments, but none of these mismatches are in themselves considered disorders, although they are certainly *risk factors* for developing disorders. The early age of puberty is mismatched to the age of social maturity in our complex society, and

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the evolved age of optimal female fertility is mismatched to social pressures for later childbearing to meet demands for lengthy education and establishment of a career prior to childbearing, yet these evolved mismatches are not considered disorders. Sleep researchers believe that there is normal variation both between individuals and within an individual's life span in the nature of a person's synchronization of sleep with their circadian rhythm, such that some people are naturally (to put it colloquially) "morning people" and some are naturally "night people," and it is generally accepted that night people are painfully disadvantaged and mismatched to our 9-to-5 work culture and especially our school system that generally starts even earlier (adolescents are disproportionately night people), but this mismatch, which has no discernible benefit, is generally considered a normal variation and not a disorder. The natural tendency to be sedentary and an aversiveness to exercise when there is no immediate demand for activity is thought to have evolved to conserve energy but is maladaptive in our current environment in which there are few demands for vigorous physical activity, yielding excessive sedentariness, yet is not considered a disorder. To take an extreme case, even mass killers, whose wanton levels of aggression may have been adaptive in some earlier environment but are surely radically mismatched with our current social environment, are generally judged nondisordered (Knoll and Pies 2019).

Moreover, the intuitions expressed in public and professional controversies indicate that when someone believes a mismatch hypothesis, they tend to doubt the corresponding disorder attribution. In fact, a mismatch account is generally taken as strong evidence that there is not a disorder. For example, those who acknowledge that the symptoms associated with attention-deficit/hyperactivity disorder (ADHD) are seriously problematic in today's school environment but think that such childhood rambunctiousness and exploratory urges are part of the normal range of naturally selected childhood inclinations—and thus are not generally a dysfunction of impulse control and attentional mechanisms—do *not* tend to see such problematic behavior within our mismatched school environment as a disorder. Rather, they argue just the opposite, that if the problem is a mismatch between evolved childhood behavior and our educational practices, then we are oppressively diagnosing and medicating nondisordered children and should change the school system. This points to one reason why the difference between disorder and mismatch is fundamentally conceptually important—namely, they suggest different priorities or options for intervention.

The most troubling problem with the mismatch account of disorder is that it undermines one of the basic goals of an analysis of mental disorder, namely, to respond to the antipsychiatric critique by distinguishing socially deviant, disapproved, or undesirable conditions from legitimate psychiatric disorders. This goal is undermined because most mismatches between the evolved nature of individuals and the current environment that come to attention of mental health professionals are precisely the kinds of mismatches with current social demands and values that the antipsychiatrists accused

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psychiatry of pathologizing. Consequently, embracing mismatches as disorders elevates social demand into a potential arbiter of disorder. Many of the absurd diagnoses that we deride as oppressive historical misattributions of disorder would potentially become disorders under the mismatch hypothesis. Soviet dissidents diagnosed with "sluggish schizophrenia," runaway slaves diagnosed with "drapetomania," and masturbating or nocturnally emitting Victorian youths diagnosed with "spermatorrhea" were all engaging in evolutionarily normal behavior mismatched to their social environments and thus legitimately diagnosable as disordered according to the mismatch approach. The fact that confusing mismatches such as social deviance with disorder undermines the medical legitimacy of psychiatry is reflected in the *Diagnostic and Statistical Manual of Mental Disorders*'s (*DSM*'s) explicit statement in the definition of mental disorder that social deviance—a salient form of mismatch between evolved normal variation and social demands—is insufficient for disorder unless there is also a dysfunction: "Socially deviant behavior (e.g., political, religious, or sexual) and conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflict results from a dysfunction in the individual" (American Psychiatric Association 2013, 20).

Garson of course focuses specifically on evolutionary mismatches, because those offer potential counterexamples to the HDA. However, momentarily casting a wider net, it is worth noting that a general mismatch criterion for disorder makes no sense because mismatches between people's natures or their early learning and their current environments are unfortunately omnipresent in life—and in fact are not in themselves considered disorders. Immigrants who do not speak the local language, kids who are the first from their families to go to college and don't know the implicit social rules for that environment, people who need a job but don't have the required skills or personal attributes to successfully fill the available openings, people desirous of a relationship but unattractive by social standards, and individuals who have irreconcilable differences with their partners would all be considered disordered if mismatches alone warranted disorder attributions. Casting a wider net only casts further doubt on the mismatch account.

In sum, the thesis that evolved mismatches fall under the concept of disorder is incorrect conceptually as reflected in both lay and professional community judgments. It is also self-defeating in terms of the goal of understanding psychiatry as a legitimate medical discipline.

Second Version: The Modal Mismatch Argument

Garson's second version of the mismatch objection may initially look like just a more technically stated version of the first version, and it does build on some of the same points made in the first version's passage above, but it is quite different. After presenting the basic evolved mismatch argument above, he says,

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> Let me clarify what I take to be the strongest form of the evolved mismatch argument. I am *not* claiming that any particular mismatch hypothesis is true. Rather, the best argument is a modal one, and I will summarize it in four sentences: it is empirically plausible that some mental disorders represent mismatches, not dysfunctions. Therefore, it is logically possible that the same is true. But the HD analysis implies that this claim is logically impossible. So, the HD analysis is wrong.

This is a common objection to the HDA—namely, why couldn't we just empirically discover that some disorders are naturally selected nondysfunctions that are very harmful in our current environment, disproving the HDA's dysfunction requirement? There are two novel things to notice about this modal argument. First, as Garson indicates, relocating the objection to the modal realm allows him to remain entirely neutral on all factual matters, thus to avoid commitments regarding the existence of any specific actual mismatches, such as those presented above. Second, the modal argument can be understood as claiming not that problematic mismatches in general are classifiable as disorders (which is how I interpreted the first version, above) but rather that it is possible that *some* mental disorders are mismatches. Consequently, identifying mismatches that are not disorders, as I did above to obtain counterexamples to the general claim that mismatches are disorders, will not defeat Garson's modal argument. The question is not whether mismatches are generally disorders but whether, in association with certain other properties such as severity, some mismatches can be disorders.

When Garson says that "it is empirically plausible that some mental disorders represent mismatches, not dysfunctions," that appears to directly beg the question at issue. To be non-question-begging, it must mean that it is empirically plausible that *some conditions currently classified as mental disorders* represent mismatches rather than dysfunctions. If the baseline is *DSM-5* categories and diagnostic criteria, this is very likely true. Given our inability to directly identify most mental dysfunctions, some *DSM-5* symptom-based diagnostic criteria sets almost certainly pick out mixtures of dysfunctions and mismatches that have similar presentations. However, according to the HDA, the mismatches are false-positive diagnoses and not genuine psychiatric disorders, even if currently misclassified as disorders. So, the question in deciding between the HDA and mismatch accounts is whether conditions currently categorized as disorders that are identified as mismatches would continue to be considered disorders.

This line of thought reveals that there is a crucial suppressed premise in Garson's modal argument: *For at least some conditions that are currently considered mental disorders, if it were established that the condition is due to an evolutionary mismatch and not to a dysfunction, then the condition would continue to be considered a mental disorder.*

There are two ways that Garson's crucial suppressed premise can be secured, and Garson implicitly addresses both. One way is by arguing that some disorders are so obviously and manifestly disorders that they would not change in disorder status no matter what we found out about their etiology. The other way is by an empirical

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evaluation of what actually happens when we discover that purported disorders are mismatches. I consider the viability of each of these in turn.

The Theoretical Argument: Are There Bona Fide Mental Disorders That Would Continue to Be Classified as Mental Disorders No Matter What We Found Out about Their Etiology?

The theoretical approach to supporting Garson's suppressed premise is to claim that, of the conditions now considered disorders that could possibly turn out to be mismatches, some are so obviously disorders on grounds of their symptomatic phenomenology that they would continue to be considered disorders no matter what theory about their etiology we might come to hold. This move is implicit in Garson's specification that he is discussing only the most "severe" and "devastating psychiatric ailments" and when in the course of his argument he calls the conditions he is considering "bona fide disorders" and "paradigmatic disorders," thus suggesting their irreversible disorder status, and explicitly when, in discussing the example of depression, he asserts that "depression, particularly when severe enough to lead to hospitalization or suicide attempts, constitutes a paradigmatic mental disorder, regardless of how it happened to evolve." If so, and if some disorders might turn out to be mismatches and not dysfunctions (as I am agreeing they might), then his suppressed premise, his modal argument, and his anti-HDA conclusion are secured.

The problem with this claim is that it is plainly false. There are simply no conditions—not severe depression, not schizophrenia, not psychopathy—that are so indefeasibly considered disorders that no new information about their etiology could persuade us differently. Disorder judgments are inherently fallible etiological explanatory-sketch hypotheses postulating dysfunction. "Bona fide" or "paradigmatic" disorders can be understood as conditions for which it is most difficult to imagine the possibility of an etiological pathway that does not involve dysfunction. But when people do imagine such possibilities, they also imagine that the condition is not a disorder.

Garson's claim that there are "bona fide" or "paradigmatic" disorders" that are so clearly disorders that no discoveries about their evolutionary etiology could lead informed observers to question that they are disorders represents a lack of historical and cultural perspective. Even those conditions considered the most severe mental disorders, such as schizophrenia and severe depression, have been claimed by serious and thoughtful theorists to be nondisorders on the basis of views that denied the presence of internal dysfunction. (I leave aside here the mistaken claims of Thomas Szasz [1974] that mental disorders do not exist because dysfunctions must consist of physical lesions and no such lesions have been identified.) For example, both R. D. Laing (1968) and a school of thought in family dynamics (Bateson et al. 1956) famously claimed that schizophrenia is a normal response to an abnormal family environment or to

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"double-binding" family communication patterns, respectively, rather than a medical disorder. Many theoreticians have claimed that some or all depression is a biologically designed response and thus not a disorder (e.g., Andrews and Thompson 2009: "the impairments associated with depression are usually the outcome of adaptive tradeoffs rather than disorder" [623]; Nesse 2014: "Is depression an adaptation … or a pathological state?" [14]) (see also the discussion regarding depression in Garson's paper). Behavioral theorists, on the basis of their learning-based theories of psychological functioning, have often denied the existence of any genuine mental disorders in the medical sense on the grounds that the etiology of all behavioral conditions is normal learning, albeit sometimes occurring in abnormal environments or in ways that violate social rules and so yield problematic behaviors (e.g., Ullman and Krasner 1969).

Nor is it the case, as Garson's passage suggests, that the "severe" or "devastating" nature of a condition makes it a bona fide disorder. There are many devastatingly severe conditions that are not considered disorders simply because they are understood to be part of human biological design. Sleep is presumably the most overall disabling condition of the human species, taking away one-third of our lives in a state of incapacity, periodic hallucination, and partial paralysis; grief is one of the most devastating emotional pains one can suffer; fatigue with extended exertion costs us the ability to function effectively under continuing physical demand; childbirth pain is often claimed to be the worst pain women feel in their lives, and advanced pregnancy is extremely impairing of basic physical capacities; and infancy and young childhood entail almost total dependence on others. Yet, none of these "devastating" conditions are considered disorders because they are judged to be part of human biological design.

Garson cites suicidality as a compelling indicator of disorder, but that is because we implicitly take it as a compelling indicator of failure of normal biologically designed human functioning. When that link is cast into doubt, the inference to disorder is also cast into doubt. Suicide over disappointed love was surprisingly common in some periods of history, and suicide over issues of honor, pride, shame, or guilt continues to occur in many cultures, yet these are not necessarily considered mental disorders because we understand how normal human emotions within a certain kind of cultural background could generate such behavior without there being a failure of biological design anywhere in the causal chain. Suicidality can be a rational choice to escape from physical or emotional pain, an avoidance of the implications of a horrific medical diagnosis, a call for help, an altruistic act in defense of loved ones or one's country, or an inclusive fitness-motivated act analogous to an organismic-level form of cellular apoptosis. So, yes, it is *conceptually conceivable* that even severe suicidal immobilizing depression could be a nondisordered state, just like extreme immobilizing grief and just like the periodically immobilizing phenomenon of sleep—which leaves the individual unable to pursue survival and reproduction activities and vulnerable to predation—are nondisorders. Severe depression as a nondisorder of course strikes Garson—and most

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of the rest of us—as deeply counterintuitive because, unlike grief and sleep, our background knowledge is such that the idea that it is not a dysfunction appears absurd on its face, as it has to physicians since antiquity—but that is not to say it is evidentially indefeasible.

The Empirical Argument: When Bona Fide Mental Disorders Are Discovered to Be Mismatches and Not Dysfunctions, Are They Still Considered Mental Disorders?

The second way to try to support Garson's suppressed premise—that if conditions considered disorders were discovered to be mismatches, they would still be considered disorders—is by examining what actually happens in the rare instances that such switches of etiological theory occur. My claim—and the prediction that follows from the HDA—is that when a condition believed to be a disorder is found to be due to a mismatch, then—modulo inertia and pragmatic considerations—there will be a tendency to reclassify the condition as a nondisorder.

Garson acknowledges the admirable riskiness of this prediction: "I applaud that Wakefield is willing to make a risky prediction and I wish more philosophers would do the same." Nevertheless, he of course thinks my risky claim is false and tries to reveal its absurdity by formulating my prediction using one of the "severe" conditions that he mentioned earlier as an example: "Wakefield is committed to the following prediction: *if* researchers and clinicians were to generally accept that a certain condition (say, antisocial personality disorder) is an evolved mismatch, *then* they would stop labeling it a 'disorder.'"

Now, the standard example I have used in support of my claim is the recent history of thinking about fever, which illustrates that even a "paradigmatic" disorder is reclassified as a nondisorder if it is discovered to be naturally selected features. At one time, fever was thought to be a paradigmatic physical disorder that was caused by toxic products of infection. Indeed, infections of various inferred etiologies and origins were often simply distinguished as etiologies of fever as the prime pathology, as in "typhoid fever," "yellow fever," "scarlet fever," "Congo fever," "dengue fever," "Lassa fever," "San Joaquin Valley fever," "West Nile fever," "Rocky Mountain spotted fever," "Parrot fever," "cat-scratch fever," and literally scores of others. However, once it was discovered that the "bona fide" and paradigmatic" disorder of fever is in fact a sophisticated biologically designed defensive response to infection—the body's raised temperature during a fever is actually regulated to be at the higher level using complex feedback mechanisms just like normal temperature and will tend to return to the fever level if artificially lowered—fever was reclassified as a nondisordered reaction and the guidelines for management rethought.

However, Garson rejects the fever example as a proper test of my claim on the grounds that it is not a pure mismatch example because of fever's potential beneficial

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effects in fighting infection: "I am not entirely convinced by this example, since what we discovered about fever is that it is beneficial for us. It is not a mismatch at all. So, I don't think we can use the fever example to draw inferences about an evolved mismatch case." In fact, the degree of fever's actual benefit under most circumstances in our current pathogen environment remains unclear, and I would maintain that surely fever's clear status as a complexly biologically designed feature would be sufficient to eliminate it from the disorder category even if it had no current benefits, but Garson does have a point. Similarly, Garson rejects the empirical evidence generated by my studies of clinical judgment of conduct disorder (Wakefield et al. 2002; Wakefield et al. 2006), which showed that conditions that satisfy *DSM* diagnostic criteria for conduct disorder and are usually judged disorders are judged to be nondisorders when the symptoms are due to understandable reactions to circumstances rather than an internal dysfunction. Again, his rationale is that the environmental circumstances described in the clinical vignettes show that given those circumstances, the symptoms benefited the described youths, and thus the behavior was not a pure mismatch without benefit. Note, however, that even if Garson's argument that these are not pure mismatches is accepted, these examples of reversal of disorder judgments do at least show that paradigmatic disorders can be reclassified.

Suppose the fever example is rejected and we accept Garson's ground rule that conditions with significant ongoing benefits don't count as mismatches. Are there then any other examples of newly hypothesized pure mismatches by which we can test my risky claim?

Happily, there is now a more conclusive test of my claim in which my prediction has been confirmed in a natural conceptual experiment. Remarkably, this test involves the very same paradigmatic severe disorder that Garson uses to illustrate the unlikelihood that my prediction will be confirmed, namely, antisocial personality disorder or "psychopathy." In recent research, it has been argued that adolescent-onset conduct disorder—as opposed to early-onset conduct disorder—is due to a mismatch between budding adolescent development and our cultural rules regarding adolescents. Similarly, moderate adult psychopathy has been argued by some researchers to be a naturally selected human variant that was advantageous in the past but is mismatched with the current social environment, and researchers have empirically tested this evolutionary hypothesis. Note that these researchers agree that both conduct disorder and psychopathy are maladaptive in our present environment, so current benefit or current adaptation is not an issue here. In both the conduct disorder and psychopathy cases, researchers concluded that if the mismatch hypothesis is correct, then the condition is not in fact a mental disorder after all. In fact, researchers who study psychopathy basically see the mismatch and disorder accounts as conflicting rival hypotheses. (In my reply to Cooper in this volume, I review this research on conduct disorder and psychopathy.) To demonstrate the sharp distinction that researchers draw between disorder and mismatch hypotheses and the inclination of those who accept the mismatch

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theory to reverse the field's earlier disorder attribution, I offer the following series of quotes from various authors in the psychopathy literature:

> (1) Adolescence-limited antisocial behavior is not pathological behavior. … The origins of adolescence-limited delinquency lie in youngsters' best efforts to cope with the widening gap between biological and social maturity. (Moffitt 1993, 692)

> (2) Is sociopathy an adaptation or an abnormality? … Because a behavior, trait, or mechanism may have evolved for its adaptive value does not imply necessarily that it is still adaptive in the current environment. … Thus, something may be an adaptation without being adaptive. … Sociopaths … clearly have both social and psychophysiological "deficits" if the standard we use is the nonsociopath. … If sociopaths are not a type designed by natural selection to fill a particular niche, then we could probably agree that they do not function normally; but if they are a type, then … the medical model is no longer appropriate. (Mealey 1995, 583–584)

> (3) From an evolutionary perspective psychopathy seems to be an adaptation rather than a disease. (Kinner 2003, 67)

> (4) Two models have guided the study of psychopathy. One suggests that psychopathy is a psychopathology, i.e., the outcome of defective or perturbed development. A second suggests that psychopathy is a life-history strategy of social defection and aggression that was reproductively viable in the environment of evolutionary adaptedness (EEA). These two models make different predictions. (Lalumiere et al. 2001, 75)

> (5) On any such "selectionist" model, psychopaths are certainly different than the rest of us, biologically speaking. However, they are not, in any biological sense, disordered. (Reimer 2008, 187)

> (6) The medical model attributes sociopathy to a "pathogen," in this case an emotional deficit that may be genetically rooted and physiologically expressed. … Framing sociopathy in evolutionary terms accordingly frees us from the explanatory constraints imposed by the medical model. (Machalek 1995, 564)

> (7) Psychopaths routinely disregard social norms by engaging in selfish, antisocial, often violent behavior. Commonly characterized as mentally disordered, recent evidence suggests that psychopaths are executing a well-functioning, if unscrupulous strategy that historically increased reproductive success at the expense of others. … Mental disorder and adaptation accounts of psychopathy generate opposing hypotheses. These results stand in contrast to models positing psychopathy as a pathology, and provide support for the hypothesis that psychopathy reflects an evolutionary strategy. (Krupp et al. 2012, 1)

> (8) In a recent study, we found a negative association between psychopathy and violence against genetic relatives … and argued that it failed to support the hypothesis that psychopathy is a mental disorder, suggesting instead that it supports the hypothesis that psychopathy is an evolved life history strategy. (Krupp et al. 2013, 1)

These experts take evolved mismatch to be in conflict with a pathology attribution, and their belief that psychopathy is likely a mismatch has caused them to reject the universal prior assessment of psychopathy as a disorder. This literature demonstrates

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that presumed disorders found to be due to evolutionary mismatches will be reconceptualized as nondisorders, and it decisively falsifies Garson's crucial suppressed premise using an example that Garson himself put forward. The HDA's risky prediction is thus confirmed in this test case. I assume that Garson will be even more admiring of my risky prediction now that it has been confirmed in an instance he set out as a test case.

There are other examples of dynamic reversals of disorder attribution when mismatch hypotheses are accepted. For example, ADHD would seem to be a paradigmatic disorder and its symptoms to have no benefit in our current constraining school environments. So, we might ask: What would happen if children with bona fide disorders of ADHD turned out to have a naturally selected gene for exploration and novelty seeking that is incompatible with contemporary school discipline but was adaptive in the nomadic environment in which humans evolved, thus indicating that in their cases the condition is a mismatch? Or, what if children who are the youngest in their school classes were found to get diagnosed at higher rates with ADHD, implying that the developmentally least mature students, who possess less inhibitory control than older children in the same grade as a matter of normal developmental variation, are being diagnosed with a disorder because this developmental variation is mismatched with school demands relative to older children in the same grade? These are both recently discovered forms of actual mismatch (Eisenberg et al. 2008; Evans et al. 2010; Zoega et al. 2012). As far as we know, there is no benefit in our current environment for these genetic or developmental variants that create problems in school. As the HDA predicts, those who made these discoveries and those who have accepted them as demonstrating mismatch rather than dysfunction tend to reject the notion that the children in question have a genuine mental disorder of ADHD, and some experts have publicly reversed their disorder attribution in such cases. (See my reply to De Vreese in this volume for further discussion of these examples and the response to them.)

In sum, the modal version of the evolved mismatch objection fails because its crucial suppressed premise—that conditions judged to be disorders will still be judged to be disorders if they are found to be due to evolved mismatches—is false.

Third Mismatch Version: The Developmental Mismatch Objection

I have responded above to the standard evolutionary mismatch objection to the HDA, to Garson's modal version of that objection, and to the modal argument's implied claim that once we have identified certain "bona fide" disorders, they will continue to be considered disorders no matter what we come to believe about their etiology. Although I will continue to comment on the evolutionary mismatch claims, I will now focus on Garson's primary innovation, his attempt to strengthen the mismatch objection by claiming that "developmental mismatches"—a concept to be explained shortly that has emerged from recent evo-devo theory in the area known as Developmental

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Origins of Health and Disease (DOHaD)—provide intuitive counterexamples to the HDA that are endorsed by researchers. Garson repeatedly cites the publications of the leading DOHaD theorists, Gluckman and Hanson (2006a; Gluckman et al. 2016) and their colleagues, as expressing such anti-HDA intuitions. I focus primarily on their work and briefly consider other authors cited by Garson at the end.

Although Garson applies the modal argument and makes the "bona fide disorder" assumption in his discussion of developmental mismatches, I mostly leave those aspects aside as irrelevant here. The "bona fide disorder" notion has been adequately refuted above; disorder claims always involve etiological explanatory sketches and can be revised if etiological theories are revised. As to the modal argument, no such relocation to the realm of possible judgments is necessary because Garson claims that the DOHaD theorists he cites actually do judge developmental mismatches to be both naturally selected nondysfunctions and disorders. If he is portraying the literature correctly, then we are dealing here not with possibilities but with actual judgments that pose a conceptual challenge to the HDA, whether or not they turn out to be true.

Recall that Garson applauds my willingness to make risky predictions and that in the case of evolutionary mismatches, my risky prediction (that once a disorder was confirmed to be a mismatch, it would no longer be considered a disorder) was confirmed in the psychopathy and ADHD examples. Garson's further claim that leading DOHaD theorists consider developmental mismatches to be disorders demands an even more risky prediction. Rather than trying to explain away these pathbreaking experts' judgments as unreflective, confused, pragmatic, or otherwise spurious, I venture the prediction (perhaps foolishly given what I know of Garson's careful scholarship!) that Garson misinterprets his own sources. The cited DOHaD theorists, I hypothesize, do not in fact understand developmental mismatch as disorder and have views more consistent with the HDA than Garson suggests. I thus now turn to Garson's cited sources and closely examine the evidence for how they think about disorder and mismatch. Due to this unorthodox response, I amply document each of my findings with textual quotes.

What, then, are the basic claims of DOHaD theory, and what are developmental mismatches and how do they differ from the standard evolutionary mismatches considered earlier? The DOHaD literature concerns the fascinating phenomenon of biologically designed choice points in prenatal developmental programming that are oriented toward adapting to a predicted later environment. The idea is that there are naturally selected forms of early developmental plasticity in which the developing organism samples the environment and, based on what it finds, selects a developmental trajectory from among multiple potential trajectories that becomes irreversibly fixed once selected. The selected trajectory represents not just an adaptive reaction to the current environment but a predictive adaptive response (PAR) to that potential anticipated type of environment in the future: "We define PARs as a form of developmental plasticity that evolved as adaptive responses to environmental cues acting early in the life

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cycle, but where the advantage of the induced phenotype is primarily manifest in a later phase of the life cycle. The cue … induces changes in the developmental trajectory of form and function such that the organism presets its physiology in expectation of that physiology matching its future environment" (Gluckman, Hanson, and Spencer 2005, 527). The cues in the human case consist largely of maternal signals of nutrition and stress via placental inputs detected by the fetus: "The fetus predicts its postnatal environment based on maternal cues transduced via the placenta and sets its physiological homeostatic mechanisms to match that postnatal environment" (Gluckman, Hanson, Spencer, and Bateson 2005, 673). Each of the fetus's potential adult phenotypes represents a naturally selected adaptation to a specific anticipated adult environment (e.g., high vs. low nutrition), and once it is selected during a limited critical-period developmental window, the trajectory is permanently fixed irrespective of the actual nature of the later environment: "One part of the reaction norm may be associated with better survival in one type of environment, while another is better suited to a different environment. … Developmental plasticity can act early in life to change the course of development, leading to irreversible trajectories that manifest as different phenotypes. … There are critical windows for plasticity in different systems. … An environmental influence may have a lifelong impact if the cue acts during the critical developmental window, but will not have analogous effect if acting outside this window" (Gluckman and Hanson 2006c, 33–34).

DOHaD theorists emphasize that PAR mechanisms are naturally selected adaptive responses, not random events or dysfunctions resulting from developmental pathology: "These are not simply the effects of constraint in utero, but rather mechanisms by which the fetus uses an early environmental cue to 'predict its future' and adopts a developmental pathway that might best suit it to its expected postnatal or adult environment. … The evolution of the ability to mount a predictive and adaptive plastic response will probably depend on a number of features, such as the accuracy of the cue and the frequencies of the various environmental states, as well as the consequences of a mismatch and the intrinsic costs of plasticity itself" (Gluckman, Hanson, Spencer, and Bateson 2005, 673); "As the nutritional environment is the most critical for species survival, it is not surprising that the systems most likely to be programmed are those associated with metabolism, growth, reproduction and coping with stress. Provided that across a species the prediction is more often right than wrong, the genetic infrastructure of PARs … will be positively selected during evolution" (Gluckman and Hanson 2006c, 41); "In mammals, an adverse intrauterine environment results in an integrated suite of responses, suggesting the involvement of a few key regulatory genes, that resets the developmental trajectory in expectation of poor postnatal conditions" (Gluckman, Hanson, and Beedle 2007, 1).

To get the flavor of developmental plasticity and PARs, consider some fascinating examples of irreversible developmental trajectories selected early in life. The axolotl

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"chooses to be either aquatic or amphibious depending on the availability and size of fresh-water ponds during early development." In the tiger snake, "jaw size is matched to prey size, a feature determined not by genetics but by exposure during the neonatal phase to prey of different sizes." And, in the desert locust, "the choice of wing and metabolic phenotype is determined in the larval phase in response to a pheromonic signal from the mother at egg-laying about population density. The wing shape and metabolism will be set for a migratory form if the population density is high and for the solitary non-migratory form if the density is low" (Gluckman and Hanson 2006c, 34, 36).

Garson focuses on another example, a small lake-dwelling crustacean, *Daphnia*: "*Daphnia* provides a remarkable example of developmental plasticity. … If a *Daphnia* is raised in the vicinity of predators, it grows a tough, helmet-shaped head. This 'helmet' is a boon as it makes it difficult for predators to swallow it. The helmet, I take it, is an adaptation designed by natural selection to protect the *Daphnia* in perilous waters … triggered by the presence of kairomones, a kind of hormone released by the predator. … There are some drawbacks to the 'helmet' phenotype. First, helmets are metabolically expensive; they require more calories to maintain. Second, the large head reduces the *Daphnia*'s mobility. That is why natural selection gave the *Daphnia* a certain degree of morphological flexibility. It only grows the helmet if it needs to. Once a phenotype is selected—'helmet' versus 'normal'—reversibility is limited. … Something inside the *Daphnia* encodes a conditional rule: 'if predators, then helmet; if no predators, then no helmet.'"

When the PAR's "prediction" goes awry, this yields a *developmental mismatch* between organism and environment. Whereas the evolutionary mismatches considered earlier occur when our biologically designed nature that was adaptive in our species' earlier environment is confronted with a novel environment, a developmental mismatch occurs when the predicted environment that triggers the organism's PAR is not the actual environment that the organism comes to confront in adulthood. Developmental mismatches can occur for a great variety of reasons. The prediction can be inaccurate either because of maternal deviations from the existing environment (e.g., lower nutrition due to poverty), maternal pathology that alters placental input, or changes in the environment between the fetal and adult stages (e.g., extreme richness of the Western diet): "Predictions may be erroneous if the fetus is exposed to an impaired fetal environment and thus receives maternal/environmental cues that are not representative of the actual environment, leading to inaccurate predictions and adoption of an inappropriate developmental trajectory. In humans and other mammals, the causes of such an impairment may be pathological, for example due to maternal or placental disease, or physiological, involving factors such as poor maternal nutrition (e.g. a hypocaloric or low-protein diet), maternal stress, or maternal constraint. … The discordance between the predicted versus actual environment during later life, known as developmental mismatch, may lead to a physiology that is unsuited to coping with the mature

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environment. The fetus that predicts an energy-poor environment but grows up in an environment with an abundance of food may lack the capacity to adjust and hence be more vulnerable to disease development. … The size of the adverse effects is dependent on the degree of mismatch and other determinants of variation" (Low, Gluckman, and Hanson 2012, 654). Moreover, the PAR mechanism is designed to work for a range of inputs and a range of environments that were common during the evolution of the organism's species and may not be able to adaptively respond to extreme inputs at the fetal stage or extreme later environments that are outside the expectable ranges.

We now finally come to Garson's formulation of a challenge to the HDA based on the possibility that standard mental disorders might be found to be developmental mismatches. First, here is how he describes the problem of developmental mismatch using his *Daphnia* example: "Suppose we hatch some *Daphnia* eggs in a tank swarming with predators, and they grow the helmet-shaped head. Suppose we then remove the predators from the tank. Then the *Daphnia* experience only the disadvantages of the helmet phenotype and none of its perks. Their condition becomes *chronically maladaptive*. It would be acutely troublesome for them if we forced them to compete over limited resources with their 'normal'-shaped counterparts, who need less food and can get to it faster."

Such developmental mismatches, Garson claims, are not dysfunctions and, if disorders, pose a challenge to the HDA:

> Here is an intuition that I have. … It seems to me that talk of "dysfunction" is out of place when it comes to developmental mismatches. Let me clarify. Suppose there is a member of *Daphnia* that chose the "wrong" phenotype; that is, suppose it was raised in a tank with predators, it grew the helmet-shaped head, and later, the predators were removed. It exhibits a developmental mismatch and it takes a fitness loss as a result. In my opinion, this does not represent an inner "dysfunction." Put metaphorically, nothing "went wrong" inside that *Daphnia*. Its developmental machinery is operating exactly as it is "supposed to." It is neither defective nor diseased; it's just unlucky. (Of course, the mismatch can *cause* a dysfunction, for example, if the *Daphnia* dies of malnutrition. But that sort of dysfunction is incidental to the mismatch; having a mismatch does not logically imply dysfunction.)
>
> This brings me to the central question of the chapter. What if some of our current psychiatric ailments result from developmental plasticity, *rather than* dysfunction? In other words, what if, in certain individuals with bona fide mental disorders, the disorder represents a developmental mismatch, much like a helmet-shaped *Daphnia* in a predator-free environment. … Such mismatches can be chronically maladaptive for the individuals that possess them. … I do not know whether this budding research program—sometimes known as Developmental Origins of Health and Disease (DOHaD)—will ultimately be vindicated (see Gluckman and Hanson 2006a for an overview). But I think it represents an exciting new avenue for exploring the roots of major mental disorders. This conjecture—that *some mental disorders are developmental mismatches*—raises a significant problem for Wakefield's "harmful dysfunction" (HD) analysis of mental disorder, which holds that all mental disorders stem from biological dysfunctions.

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So, Garson claims that developmental mismatches—either all or some—are not dysfunctions but are still disorders. As we saw earlier regarding the "bona fide disorder" notion, one cannot rely on the current classification of a condition as a disorder to establish how the condition would be considered if new discoveries were made about its etiology. So, to evaluate Garson's claim that developmental mismatches are nondysfunctions that are disorders, we have to examine how DOHaD theorists actually consider their proposed mismatches.

Note that with respect to the one mismatch that Garson says the most about—namely, the *Daphnia* that develop burdensome helmets but then confront an adult environment without the predators from which the helmets are designed to protect them—it appears that Garson goes against his own claim and dismisses the condition as a nondisorder. Garson says that his intuition is that the maladaptive helmets are not a dysfunction because development proceeded as biologically designed, and I agree. Garson's argument against the HDA depends on such cases nonetheless being disorders, but in the *Daphnia* case, Garson does not say that. Instead, he says, "Put metaphorically, nothing 'went wrong' inside that *Daphnia*. Its developmental machinery is operating exactly as it is 'supposed to.' It is neither defective nor diseased; it's just unlucky." I take it that the phrase "neither defective nor diseased" is equivalent to "neither dysfunctional nor disordered." Garson's intuition here seems to be consistent with the HDA and seems right on its face: the *Daphnia* is normal but maladaptively mismatched to its environment, and that might cause a disorder but it is not a disorder. Garson notes that the *Daphnia* "takes a fitness loss" due to the mismatch, but a fitness loss is not a disorder. The DOHaD literature repeatedly cautions that reduced fitness in an environment is not the same as reduced health. Indeed, Gluckman et al. (2016) list as one of the "Fundamental Principles of Evolutionary Medicine" that "selection operates to enhance fitness, not primarily to enhance health or longevity" (162) and reiterate that "selection operates to enhance inclusive reproductive fitness, not necessarily health" (175). In sum, the same reasoning that Garson applies to the mismatched *Daphnia*—that it is neither dysfunctional nor disordered—should apply to all evolutionary and developmental mismatches.

The primary evidence Garson presents for his claim that developmental mismatches are or can be disorders—indeed, other than his own intuition, which he acknowledges might be idiosyncratic, the *only* evidence he presents—consists of his repeated assertion that leading theorists in the DOHaD field judge such mismatches to be disorders: "Some psychiatric researchers take this possibility [i.e., that some disorders are developmental mismatches] quite seriously. … Such mismatches can be chronically maladaptive for the individuals that possess them. … I do not know whether this budding research program—sometimes known as Developmental Origins of Health and Disease (DOHaD)—will ultimately be vindicated (see Gluckman and Hanson 2006 for an overview)"; "several researchers have endorsed mismatch hypotheses for various disorders,

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and they seem to believe, judging by their terminology, that the conditions they study are, in fact, 'disorders' (or 'pathologies,' 'diseases,' etc.) (e.g., McGuire and Troisi 1998; Gluckman and Hanson 2006a; Glover 2011)"; "Moreover, as I indicated above, the few people who have endorsed the claim that some mental disorders are developmental mismatches seem to describe those conditions as 'disorders,' 'pathologies,' and so on (as I indicated in the previous section; e.g., Gluckman and Hanson 2006a)." So, the most direct way to test Garson's claim is to examine whether leading DOHaD theorists do conceptualize developmental mismatches as disorders.

One might interpret Garson's claim in either of two ways. First, there is the stronger general claim that DOHaD theorists conceptualize developmental mismatch as itself conferring disorder status. Alternatively, one might make the weaker claim (along the lines of Garson's "bona fide disorder" argument) that DOHaD theorists would allow that when conditions already considered disorders are discovered to be mismatches, those are cases of developmental mismatches that are disorders. It is not entirely clear which thesis Garson is defending, so I address both.

There are three critical points that I document below in response to these claims. First, throughout their writings, DOHaD theorists consistently distinguish pathology from risk factors for developing pathology and insist that an evolutionary or developmental mismatch between organism and environment is not a pathology or disorder in its own right but a risk factor for developing pathology. Second, the available evidence indicates that these theorists hold that when a condition widely considered to be a disorder is found to be an evolutionary or developmental mismatch, the disorder label is a mistake and the condition should not continue to be medicalized but should be understood as a normal variation that is problematic only due to the mismatched environment in which it occurs. Third, there is a distinction between developmental mismatches due to evolved PAR mechanisms and mismatches due to various dysfunctions of development, and the DOHaD literature recognizes such true dysfunctions and refers to them as "disruptions." It is among disruptions—which are not naturally selected trajectories and thus classifiable as dysfunctions—that disorders may be found, and this approach is consistent with the HDA. Thus, there is nothing in the cited DOHaD theorists' writings that poses a basic challenge to the HDA. I will document these points with quotes from the DOHaD literature.

First, then, it is striking that throughout the DOHaD literature, it is made crystal clear that the result of an evolutionary or PAR-generated developmental mismatch that reduces fitness is not a disorder but a normal-range naturally selected variant that, due to the problematic interactions with the environment that result from the mismatch, can create a greater *risk* of developing a disorder. The development of an actual disorder, it is explained, requires a proximal cause that constitutes a dysfunction. These points are made consistently and repeatedly across publications, as in the following passages (I add emphases to the uses of "risk" and cognates): "The fundamental assumption

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underlying the DOHaD model is that environmental factors acting in early life have consequences which become manifest as an *altered disease risk* in later life" (Gluckman and Hanson 2006c, 33); "It should be emphasized that mismatch does not cause disease, but rather *increases the risk of disease* in later life" (Low, Gluckman, and Hanson 2012, 654); "In general, we are not arguing that evolutionary processes cause disease, rather that they have important effects on the *relative risk of developing symptoms or disease*. … With respect to all that we consider in this book, it is important to think in terms of *variations or changes in disease risk* rather than viewing ultimate mechanisms as leading directly to causation of disease" (Gluckman et al. 2016, 161–162, 163); "In modern humans, such a *mismatch leads to a risk of disease*. … Because the upper limit of the nutritional environment is rising globally, the *risk of disease due to mismatch* increases even for individuals who had normal early development" (Gluckman and Hanson 2004, 1735, fig. 3); "The model suggests that a mismatch between fetal expectation of its postnatal environment and actual postnatal environment contribute to later *adult disease risk*" (Gluckman, Hanson, and Pinal 2005, 130); "Where the prediction is incorrect, however, the organism is left with a postnatal physiology that is mismatched and inappropriate, putting it at increased *risk* from predation or disease" (Gluckman, Hanson, Spencer, and Bateson 2005, 673); "Critical periods in development result in irreversible changes; if the environment in childhood and adult life differs from that predicted during fetal life and infancy, the developmental responses may increase the *risk of adult disease*" (Godfrey 2006, 6); "Early life influences can alter later *disease risk*—the 'developmental origins of health and disease' (DOHaD) paradigm. … Mismatch between the anticipated and the actual mature environment exposes the organism to *risk of adverse consequences—the greater the mismatch, the greater the risk*" (Gluckman, Hanson, and Beedle 2007, 1); "When there is a mismatch, the individual's ability to respond to environmental challenges may be inadequate and *risk of disease increases*. Thus, the degree of the mismatch determines the individual's *susceptibility to chronic disease*" (Godfrey et al. 2007, 5R, 6R); "Developmental factors play a considerable role in determining individual *disease risk* later in life. This phenomenon is known as the Developmental Origins of Health and Disease (DOHaD). … In the event of a mismatch between the early and mature environment, such anticipatory responses may become maladaptive and lead to *elevated risk of disease*" (Low et al. 2012, 650); "Generally the practice of medicine focuses on the issues of *proximate* causation—namely the actual physiological and anatomical disruptions that lead to disease, because it is these pathological processes that inform most diagnostic and therapeutic choices. … But what this book aims to demonstrate is … ultimate, that is evolutionary, pathways that affect *the risk of developing disease*" (Gluckman et al. 2016, 161); "Evolutionary processes mediate *disease risk* via multiple pathways. … The key role of evolutionary and developmental histories in influencing *disease risk* provides a framework for understanding the etiology of many noncommunicable diseases" (Low and Gluckman 2016, 69).

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These passages make clear—in direct contradiction to Garson's claim—that the DOHaD paradigm is about how early influences alter disease risk, not disease itself, and that developmental mismatch is not itself a disease but rather exposes the organism to the risk of disease where "the greater the mismatch, the greater the risk"—*not* the greater the disorder. The DOHaD literature thus agrees with the HDA that because the PAR-triggered alterations are evolutionarily selected options and are not dysfunctions, they are not disorders even if mismatched. Only dysfunctional conditions that arise from them are considered disorders.

If the strong general thesis that maladaptive evolutionary or developmental mismatches are disorders is rejected by DOHaD theorists, do they at least allow the weaker thesis, which Garson seems at times to be defending, that some mismatches that are not dysfunctions are nonetheless disorders? No doubt some evolutionists talk this way for a variety of reasons (see below). However, the evidence from the writings of leading DOHaD theorists suggests that they understand that developmental mismatch is not disorder when there is only maladaptation to an environment and no dysfunction. That is, when confronted with conditions that are widely considered disorders but that are in fact evolutionary or developmental mismatches, leading DOHaD theorists tend to argue that this is a conceptual confusion and that the condition should not be classified as a disorder. On the other hand, confronted with a disruption of development that can be construed as a dysfunction, they tend to accept that a resulting problematic condition is a disorder. Here are some examples including both developmental and evolutionary mismatches, as well as both nondisorders and disorders.

Both the earlier and later DOHaD anthologies (Gluckman and Hanson 2006a; Gluckman et al. 2016) use the condition of lactose intolerance, an evolutionary mismatch, to lay out the case that mismatches can be mistaken for disorders but should not be so considered—and the logical point would seem to apply to both evolutionary and developmental mismatches. I quote from the authors' later version of this illuminating example at some length:

> Consider a young man who presents with abdominal pain, bloating, and diarrhea. He is a recent immigrant from Southeast Asia with no history of these symptoms. He reports that yesterday he shared lunch with work colleagues during which he consumed a couple of glasses of milk and had a plate of ice cream. This was unusual for him, but his colleagues, who are of European ethnicity, were unaffected. Why is this young man made ill by ingesting a normal foodstuff?
>
> Cows' milk, like the milk of most mammals, is rich in the disaccharide lactose. The sugar transporters in the human gastrointestinal tract cannot move intact lactose across the gut wall, but babies can digest lactose because of the presence of the enzyme lactase, which breaks down lactose into easily absorbable glucose and galactose. In most humans, lactase expression in the intestine disappears after weaning, but human populations with a history of pastoralism—mostly people of northern European or East African origin—have a high prevalence of

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> mutations in the promoter region of the lactase gene, causing the enzyme to be expressed within the intestinal tract throughout life. This enables them to consume milk throughout their lives.
>
> But this young man of Asian origin does not carry the persistence mutation and therefore does not express lactase in his duodenum … his symptoms arise from a mismatch between his genetic origin—from a population where, historically, consumption of milk after weaning was unknown and lactase persistence is rare—and his current environment where milk is easily available and widely consumed.
>
> … This example is central to the purpose of this book, because Western medical textbooks often define the inability to absorb lactose as a metabolic *disorder*—adult hypolactasia—but from an evolutionary point of view this man's inability to digest lactose is *normal* and is shared with 70% of the world's population. It has only become manifest in an environment distinct from that to which he is adapted. … This concept of an organism *matched* or *mismatched* with its environment is fundamental to both evolutionary biology and evolutionary medicine, where mismatch … may lead to pathology. … The World Health Organization classifies such 'lactose intolerance' as a metabolic disorder, although in fact this trait represents the normal and ancestral human condition. (Gluckman et al. 2016, 5–6)

I take it the point is that, although the stomach problems resulting from drinking milk may be a disorder in virtue of the digestive dysfunction, this individual's inherent condition of lactose intolerance is not itself a disorder even though it is mismatched to and maladaptive in his current environment, because it is how he was biologically designed. This is analogous to Garson's *Daphnia* that was perfectly designed for an environment that unfortunately it does not inhabit—which even Garson judges to be nondisordered. The passage provocatively makes clear that the criterion of dysfunction takes precedence over maladaptation in a given environment and thus that the World Health Organization's classification of lactose intolerance in itself as a disorder should be rejected—although the manifestation of that condition in digestive dysfunction would of course remain a disorder.

Turning to developmental dysfunction, a clear example of how DOHaD theorists react to the medicalization of a mismatch with considerable psychological ramifications is provided in papers considering the trend in Western countries toward earlier puberty, especially among girls. Although the papers acknowledge that some cases of early puberty involve developmental disruptions that are true dysfunctions (e.g., brain lesions, hormonal disorders) and therefore disorders, DOHaD authors argue that the broader trend toward early puberty among girls in the developed world is due to developmental plasticity responding to various fetal influences, with an outcome that is severely mismatched to current social demands. These authors routinely and emphatically distinguish medical disorder from mismatch in their discussion of early puberty and make clear that the mismatch itself should not be confused with medical disorder. In fact, they take pains to correct what they see as a mistake by others in assuming there is a disorder when in fact there is a developmental mismatch, as in the following

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passages from two articles: "We will argue that there is a risk that early puberty is being inappropriately perceived as a medical issue rather than recognizing that there is mismatch between biological reality and the increasingly complex society in which young people live" (Gluckman and Hanson 2006d 26); "Recent decades have exposed a mismatch between the age of biological maturation and the age of psychosocial competency. … We must be careful not to inappropriately medicalize early puberty. The use of the term 'precocial puberty' to describe early puberty which does not have a pathological basis is inappropriate" (Gluckman and Hanson 2006d, 30); "In the past few decades, as puberty has advanced, biological maturation has come to precede psychosocial maturation significantly for the first time in our evolutionary history. Although this developmental mismatch has considerable societal implications, care has to be taken not to medicalize contemporary early puberty inappropriately" (Gluckman and Hanson 2006e p. 7); "There is … increasing awareness of the consequences of the psychosocial 'mismatch' which arises from early biological reproductive competence in societies in which young women do not obtain psychological or social maturity until at least their late teens. Generally, a medical approach is taken to early menarche. Here, we review evidence suggesting that the timing of puberty … can be better understood by reference to evolutionary principles. These considerations … challenge the concept that it is necessarily pathological" (Gluckman and Hanson 2006e, 7); "We have suggested that an evolutionary perspective … argues for more careful use of the term 'precocious puberty'. This term implies pathology … the vast majority of young women undergoing menarche at increasingly younger ages have normal physiology and progression of puberty; their physiology has been simply determined by their distant ancestors" (Gluckman and Hanson 2006d, 11).

Another indicator that these theorists clearly distinguish disorder from developmental mismatch occurs in the title of an inserted text box that explores various adaptive and maladaptive features of posttraumatic stress disorder (PTSD). The box is titled, "Post-traumatic Stress Disorder: Adaptive or Pathological?" (Gluckman et al. 2016, 274). By "adaptive" here, they mean adaptive not in the immediate environmental sense but in the sense that applies to PAR reactions—namely, it was naturally selected as adaptive in our species' environments of evolutionary adaptation (EEA). Their conclusion seems to be that PTSD has components that by themselves are naturally selected, but the overall configuration is a dysfunction and thus a disorder. The point is that they unblinkingly contrast adaptive with pathological, implying that naturally selected features are assumed to be nonpathological and on that basis raising the question whether PTSD should be considered a genuine disorder.

In case I am giving the contrary impression, it should be emphasized that despite the nondisorder status of mismatched PAR conditions, there is ample room for dysfunction and disorder within the developmental mismatch approach. Leading DOHaD authors distinguish normal-range environmental circumstances to which the plastic response

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is biologically designed from more extreme or pathological environmental inputs that they term developmental "disruptions" and roughly correspond to dysfunctions. They understand that this distinction is conceptually fundamental, and it is repeatedly emphasized, "These [PAR] factors act through the processes of developmental plasticity … and can be distinguished from developmental disruption" (Gluckman, Hanson, and Pinal 2005, 130); "Normal development may be disrupted by early environmental influences; individuals that survive have to cope with the damaging consequences" (Gluckman, Hanson, Spencer, and Bateson 2005, 671); "A key issue is to distinguish between factors that disrupt development and which are not regulated and those that are based on the processes of developmental plasticity and may have adaptive value. … We have to accept that some environmental exposures … simply disrupt the normal pattern of development" (Gluckman and Hanson 2006b, 2); "Extreme developmental environments lead to developmental disruption. … Within the normal range of variation … maximal fitness is conferred by the action of predictive adaptive responses" (figure 3.1 legend, Gluckman and Hanson 2006c, 37); "Not all environmental factors act during early development through these plastic processes. Some environmental influences are clearly pathological and lead to disruption of development rather than channeling development. Teratogenesis is the most obvious manifestation of pathology. … Developmental disruption may also occur at a less overt level. The change may not be in gross structure, leading to a malformation, but in the substructure or function of the organ. This change in structure or function has no adaptive value at any stage in the organism's life" (Gluckman and Hanson 2006c, 34); "Environmental factors acting during the phase of developmental plasticity can either act to disrupt the normal program of development or to modulate it. Developmental disruption may be overtly teratogenic … or may be much more subtle. Clearly, such disruptive responses cannot be considered adaptive" (Gluckman and Hanson 2006b, 3); "Developmental plasticity, which has an adaptive origin, must be distinguished from developmental disruption, which does not" (Gluckman et al. 2016, 96).

The many forms of disruption yield many pathways to developmental disorder: "Errors in prediction might arise either because the postnatal environment has shifted or because the foetus has received faulty information on which to base its prediction. The latter is most likely to happen in the presence of maternal disease or placental dysfunction, but also as a result of exaggerated maternal constraint. … Developmentally disruptive events in response to environmental stimuli irreversibly interfere with embryonic development and, depending on their nature, may have deleterious effects either in utero and/or after birth. Generally, such cues act by interfering with a developmental process during periods of vulnerability, such that structural deficits emerge. The stimulus may be a drug, ionizing radiation, a major environmental shift such as hyperthermia or hypoxia, disease, or a gross nutritional disruption" (Gluckman, Hanson, Spencer, and Bateson 2005, 672); "The fidelity of the prediction is influenced

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by … pathophysiological factors, such as maternal or placental disease or changes in maternal nutrition. … Fetal growth patterns can be affected by maternal nutritional balance within the normal absolute-intake range" (Gluckman and Hanson 2006c, 44–45); "It is possible, for example, that the mechanism which increases … vigilance in offspring becomes maladaptive when it causes a disabling level of phobia in some individuals. In light of findings that genetic changes in many different loci appear to contribute to the risk of schizophrenia, it may be that such traits generally improve cognitive fitness, but at some point reach a cliff-edge and failure" (Glover 2011, 358); "Predictions may be erroneous if the fetus is exposed to an impaired fetal environment and thus receives maternal/environmental cues that are not representative of the actual environment, leading to inaccurate predictions and adoption of an inappropriate developmental trajectory. In humans and other mammals, the causes of such an impairment may be pathological, for example due to maternal or placental disease, or physiological, involving factors such as poor maternal nutrition (e.g. a hypocaloric or low-protein diet), maternal stress, or maternal constraint" (Low, Gluckman, and Hanson 2012, 654).

This is an area in which the complexity leads to ambiguity. As Gluckman and Hanson (2006b) observe, "Evaluating whether a response is adaptive or disruptive may be difficult" (5). Even if the HDA is accepted as the correct analysis of disorder, one might find legitimate disagreement about whether, say, environmentally induced myopia or conduct disorder in response to abuse is or is not a dysfunction and thus is or is not a disorder (see the comment on indeterminacy, below). DOHaD theorists offer some more esoteric examples: "For example, is the reduction in nephron number in sheep after maternal exposure to very high doses of glucocorticoids in early gestation (Wintour et al., 2003) a process where the steroid has disrupted the normal pattern of nephron differentiation, or is it part of some adaptive process mimicking a normal situation where the fetus responds to maternal glucocorticoids crossing the placenta under situations of maternal stress? Similarly, is the continuous relationship between maternal vitamin A intake and nephron number in the rat a dose-dependent disruptive effect or does it have adaptive value?" (Gluckman, Hanson, and Beedle 2007, 5). I believe that answering these types of questions sometimes leads us to the limits of functional thinking and also may bring us to confront issues of indeterminacy of function, as Garson suggests. However, where there are reasonably firm intuitions once details are filled in, they also can illuminate the structure and scope of our concept.

Other Authors Cited by Garson

I have surveyed above the writings of the leading school of DOHaD theorists, sifting the evidence regarding Garson's claims versus the HDA as a way to explain their intuitions. Garson cites some other publications not addressed above that he thinks are congenial to his view, and they deserve comment. First, it should be kept in mind that

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in considering whether mismatches are considered disorders, one can easily be misled by the literature's casual usage of "disorder." When DOHaD theorists address conditions generally labeled disorders and especially mental disorders, they often describe the conditions as "disorders" even when discussing potential evolutionary and developmental mismatches. However, this is more terminological than conceptual. Given the great fanfare and controversy surrounding each revision of the *DSM*, and given that the *DSM* and *International Classification of Diseases* (*ICD*) are considered official listings, it is potentially confusing and no small thing to suggest that a condition listed as a mental disorder is in fact not a disorder. It is easier and safer in anything other than a conceptual-analytic context to use "disorder" just to mean "whatever is listed as a disorder in *DSM* (or *ICD*)" and proceed with one's etiological theorizing.

Other than Gluckman and his colleagues, Garson cites two references regarding mismatches being considered disorders, and both of them take this terminological route. Garson cites McGuire and Troisi's (1998) book in which they make a case for evolutionary theory as an integrating framework for psychiatry. However, this book has nothing much to say about the concept of mental disorder and takes no stand on whether developmental mismatches are disorders. Instead, the authors explicitly state that in using the term "disorder," they will simply abide by the *DSM-IV*'s listing of conditions as disorders: "We will use the term … *disorder* when we are referring to disorders specifically as they are described in the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*, 1994)" (1998, 13). Consistent with this orthodox perspective, when they later confront the question of "how disorders are defined," they simply note, "As most readers will be aware, there is no generally accepted definition. … We will not dwell on this point but will settle for the definition used in *DSM-IV*" (1998, 14) and quote the *DSM-IV* definition. So, this book's disorder attributions offer no support for Garson's conceptual claims. Note that in quoting the *DSM-IV* definition, McGuire and Troisi omit the conceptually crucial "dysfunction" sentence ("Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the individual" [1994, xxi–xxii]). This omission anticipates Troisi's (2006) later identification of disorder with reduced fitness independent of dysfunction: "A maladaptive psychological or behavioral syndrome that impacts negatively on the individual's inclusive fitness. … A dysfunctional mechanism underlying the syndrome is neither necessary nor sufficient for a diagnosis of mental disorder" (Troisi 2006, 328). This is the very position rejected as obviously wrong by leading DOHaD theorists, and it is a position that renders psychiatry helpless to respond to antipsychiatric critiques because almost any socially disapproved feature can be made fitness-reducing through social sanctions. Indeed, on Troisi's analysis, being a member of a severely oppressed minority could be a disorder.

Garson also cites Glover (2011). Glover's paper is a review that suggests that the DOHaD paradigm as developed by Gluckman and colleagues might be systematically

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extended to a broad range of psychodiagnostic variables. Glover does not directly address the nature of the disorder/nondisorder boundary and relies on *DSM* categories to label as disorders the mismatched conditions she discusses. However, Glover's reliance on *DSM* classifications to identify mismatches with disorders seems to be justified only by misidentifying maladaptiveness with disorder: "A mismatch between what was adaptive in an earlier environment and the world in which we now live can lead to pathology. Thus the outcomes which can be increased by prenatal stress or anxiety and their potential adaptive value in our ancestral environment … can be quite maladaptive in our modern environment. For example, we are not usually exposed to the type of danger for which extra vigilance (anxiety) or readily distracted attention (ADHD) would be helpful, and these symptoms can both be distressing and impede formal learning" (359). Moreover, Glover hints at lurking conceptual questions about such labels when she says things like: "The evolutionary perspective can add a new viewpoint in trying to understand the long-term effects of prenatal stress. Fetal programming may help explain why some forms of developmental psychopathology have persisted in the population. It could be of evolutionary benefit to have a minority of individuals who are more vigilant (anxious), impulsive or with readily distracted attention (ADHD), or willing to break the rules or be aggressive (conduct disorder). In times of stress it may be adaptive to have a higher proportion of the population with these traits" (364); "An evolutionary perspective may give a different understanding of children in our society with these symptoms. … The type of cognitive deficits observed after prenatal stress … may be those which were adaptive in a past environment" (356); and "Gluckman et al. (2009) make the case that concepts of health and disease are altered by taking an evolutionary perspective. Our understanding of an individual's health may depend on knowledge of their evolutionary origin and how that interacts with the modern world" (Glover 2011, 359). It is difficult to believe that when Glover says, "Thus some of the altered outcomes observed after prenatal stress may well, in their milder forms, have been adaptive in more primitive conditions" (357), that if pushed, she would insist that nonetheless these are medical disorders—but ones that could be "cured" by placing the individual in a more threatening environment! In sum, Glover's paper, like McGuire and Troisi's book, explores evolutionary perspectives on the conditions currently classified as mental disorders without stopping to reflect on the concept of disorder itself. It thus offers no serious grounds for resolving the issues raised by Garson one way or the other. The only sources cited by Garson that take this issue seriously are the ones by Gluckman and colleagues cited extensively above.

Thus, the evidence of the texts cited by Garson goes against his claims and supports the HDA. Garson demands that "at the very least, I would like to be given an independent reason for thinking that, if some … disorders result from plasticity, then they are not real disorders at all." I have provided that reason—namely, this is the best interpretation of the views of the leading theorists in the DOHaD field, and the evidence Garson

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cites to support his case is entirely based upon but mischaracterizes those views. He also says, "The HD analysis also makes a prediction about clinical usage and I have given reasons for my skepticism about that prediction." I showed in earlier comments that his skepticism about my "fever" example can be addressed by presenting other even more persuasive examples, and above I have now also shown that DOHaD theorists confirm my prediction as well, for example, in their suggesting that lactose intolerance and early puberty, both medicalized conditions, should be demedicalized because they are mismatches, and more generally in their reasoning behind those claims.

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