Eating Disorders: National Institute of Mental Health’s Perspective

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Abstract

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental and behavioral disorders through research, and eating disorders embody an important fraction of this burden. Although past and current research has provided important knowledge regarding the etiology, classification, pathophysiology, and treatment of the eating disorders, there are still significant challenges that need to be addressed. This article briefly describes some of these challenges, recent NIMH-supported research and research-related activities directed at addressing these challenges, and approaches and areas of research that hold promise for furthering the understanding and treatment of eating disorders.

Advancing the understanding and treatment of eating disorders is an issue of immense public health importance and is recognized as an area of high priority by the National Institute of Mental Health (NIMH). These disorders—which include anorexia nervosa, bulimia nervosa, and the six different eating disorders that fall under the category eating disorder not otherwise specified—generally occur during adolescence and early adulthood, often endure throughout life, and can have a devastating impact on patients and their families. Moreover, eating disorders often co-occur with other psychiatric disorders and disturbances, including depression, anxiety, obsessionality, substance abuse disorders, and marked impairments in social functioning (Flament, Godart, Fermanian, & Jeammet, 2001; Halmi et al., 1991; Kaye, Bulik, Thorton, Barbarich, & Masters, 2004). Serious cardiovascular and neurological complications as well as impaired physical development are some of the medical morbidities associated with eating disorders, and in particular with anorexia nervosa (McKenzie & Joyce, 1992; Mitchell, Specker, & de Zwaan, 1991; Striegel-Moore, Leslie, Petrill, Garvin, & Rosenheck, 2000). Within the context of anorexia nervosa, the mortality rate is 5% per decade, making it one of the leading contributors to excess mortality of any of the psychiatric disorders (Birmingham, Su, Hlynsky, Goldner, & Gao, 2005; Sullivan, 1995), and furthermore, this disorder is associated with a 50-fold increase in the relative risk of death from suicide (Keel et al, 2003).

In fiscal year 2005, NIMH provided approximately $21 million for research in eating disorders, and some of the areas of research currently being supported include genetic studies seeking to identify and localize genes that increase susceptibility to anorexia nervosa and related disorders, investigations of factors that increase the risk for and maintenance of bulimic pathology, studies using brain-imaging technologies to assess potential neurobiological abnormalities that may contribute to anorexia nervosa and bulimia nervosa, and a number of behavioral and/or pharmacological interventions for improving treatment and/or preventing relapse in eating disorder populations.

Although the majority of eating disorder research at the National Institutes of Health (NIH) is supported by NIMH, other institutes—including the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK); the National Institute of Drug Abuse (NIDA); and the National Institute of Child Health and Human Development (NICHD)—also support certain areas of research related to eating disorders. For example, NIDDK supports investigations on binge-eating disorder in which the focus is on parameters associated with obesity and weight loss.
Scientific investigations related to the intersection of drug abuse, drug dependence, and eating disorders are supported by NIDA and include studies on the etiology and potential common mechanisms underlying addiction and impulse control problems such as binge eating. Studies supported by NICHD include, in part, those targeting health risk behaviors that have their origins in childhood, including eating disorders, as well as research on the effects of children’s eating disorders on family–parent–child interactions.

Recent NIMH efforts to advance research on eating disorders include the issue of a Request for Applications announcement, “Research on Interventions for Anorexia Nervosa,” which was designed to support collaborative networks of investigators and institutions working to develop and test evidence-based treatments for anorexia nervosa. The result of this initiative was the funding of a large multisite program designed to develop and test behavioral and pharmacological treatments for anorexia nervosa. In 2006, NIMH and NICHD also issued a standing Program Announcement, “Translational Research in Eating Disorders,” which describes specific areas of research that the participating institutes want to foster. In addition to research that is supported through grants, NIMH also sponsors and convenes scientific conferences and workshops in specific areas. Within the context of eating disorders, NIMH, along with other participating NIH institutes, convened a workshop titled “Development of Research Priorities for the Treatment of Anorexia Nervosa: Overcoming Barriers” that was held to discuss the serious nature of the disorder and the obstacles that hinder progress in research on anorexia nervosa. The proceedings from this workshop were published in 2004 (Agras et al., 2004). Another NIMH-supported workshop took place in July 2006 and focused on classification and diagnosis of eating disorders. The specific goals of this workshop were to address key unresolved issues of contention in the current nosology of eating disorders; to identify existing data sets that may be of use for exploring what changes, if any, ought to be introduced in the upcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM); and to discuss the most pressing research questions related to diagnostics and classification of eating disorders. The proceedings from this meeting will be published in a forthcoming special issue of the International Journal of Eating Disorders.

The driving forces behind these and other NIMH research efforts are the public health importance of these disorders; the recognition that present-day treatments are significantly limited; and the need to identify the underlying pathophysiology of eating disorders, which will be critical for developing more effective treatments and preventive strategies. For eating disorders, there are a number of important areas of research in which additional progress is critically needed. These include, in part, epidemiology, assessment instrumentation development, classification and diagnosis, services, and research training. However, the remainder of this article briefly focuses on issues regarding current treatment limitations and obstacles, pathophysiology, and specific areas and approaches to eating disorders research that NIMH hopes to foster.

Treatments for Eating Disorders

Anorexia Nervosa

Pharmacological interventions—Medications used for the treatment of anorexia nervosa include, in part, first and second generation antidepressants and antipsychotics, opiate antagonists, and mood stabilizers (Attia & Schroder, 2005). To date, no clearly effective pharmacological treatments for restoring weight during the acute phases of anorexia nervosa (i.e., the underweight state before weight restoration) have been established (Attia, Haiman, Walsh, & Flater, 1998; Barbarich et al., 2004; Halmi, Eckert, LaDu, & Cohen, 1986), and the results have been mixed regarding effectiveness of the existing pharmacological treatments for preventing relapse in weight-restored patients (Kaye et al., 2001; Strober, Freeman, DeAntonio, Lampert, & Diamond, 1997; Walsh et al., 2006). In addition to achieving weight
restoration and maintenance, there are suggestions in the literature that some pharmacological interventions may be modestly effective in reducing other core features and comorbidities related to anorexia nervosa (Attia et al., 1998; Barbarich et al., 2004; Halmi et al., 1986).

**Psychosocial interventions**—Of the various psychotherapeutic interventions used to treat adolescents with anorexia nervosa, family-based therapies have been found to be the most effective in leading to clinically meaningful weight gain and improvements in eating and mood-related outcomes (Dare, Eisler, Russell, Treasure, & Dodge, 2001; Eisler et al., 2000; Robin, Siegel, Moye, Dennis, & Sikand, 1999; Russell, Szmulker, Dare, & Eisler, 1987). However, even though family-based treatments for anorexia nervosa have shown some positive clinical utility, it is still premature to conclude that this mode of intervention is the optimal treatment for adolescents. Given that treatment failure for anorexia nervosa is relatively higher in adults than in adolescents (Russell et al., 1987) and that the potential for recovery declines significantly after patients have been ill for more than 10 years (Strober, Freeman, & Morrell, 1997), it is clear that effective treatments targeting adolescent populations are critically needed.

In adults, the results regarding the effectiveness of a variety of psychotherapeutic interventions for treating anorexia nervosa have been variable, with no single approach demonstrating a clear advantage (Dare et al., 2001; Eisler et al., 2000). A recent and potentially promising study by McIntosh et al. (2005) reported that an intervention that combined clinical management and supportive psychotherapy developed specifically for anorexia nervosa was superior to cognitive–behavioral therapy (CBT) and interpersonal therapy (IPT). In another study with adult anorexia nervosa patients, CBT delivered posthospitalization appeared to reduce the risk of relapse (Pike, Walsh, Vitousek, Wilson, & Bauer, 2003).

Taken together, much of the existing treatment intervention literature for anorexia nervosa is limited, and effective medication and psychosocial treatments are critically needed. These problems are due, at least in part, to a number of obstacles that hinder the development and implementation of rigorous evidence-based treatments for anorexia nervosa. Some of these obstacles include anorexia nervosa’s low base rate and limited population prevalence in any single location; patient noncompliance to research protocols; high dropout rates from studies, which lead to inadequate sample sizes; limited long-term outcome results; and research methodology and design limitations. To address these obstacles, large collaborative, multisite randomized controlled trials are needed to assist in the recruitment of a sufficient number of anorexia nervosa participants, which, in turn, will be an important step in facilitating the development of novel medications and psychotherapeutic approaches targeting the primary symptoms of anorexia nervosa and in allowing rigorous evaluations of existing treatments. As mentioned above, in 2005, NIMH put forth an initiative to develop this type of collaborative, multisite research network, and the first grant focusing on treatment development for anorexia nervosa in adolescents was recently awarded. Clearly there is a need for a comparable multisite research network focusing on treatment development for adult anorexia nervosa. Within this same context, developing interventions that will result in increased treatment compliance and reduced attrition are sorely needed, as are assessments designed to determine the optimal timing for pharmacological and psychotherapeutic interventions during the acute phase of anorexia nervosa. Other key areas of research that NIMH considers critical for developing and validating evidence-based treatment for anorexia nervosa are presented in Table 1. It is important to note that the areas described in Table 1 are also relevant for bulimia nervosa and binge-eating disorder.

**Bulimia Nervosa**

**Pharmacological interventions**—Medications used to treat bulimia nervosa include, in part, first- and second-generation antidepressants, antiemetics, and anticonvulsants. To date,
the antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been the most extensively studied medication used to treat bulimia nervosa and is the only Food and Drug Administration–approved treatment for any of the eating disorders. Fluoxetine appears to be effective in reducing the frequency of binge eating and vomiting, reducing the rate of short-term relapse, and improving eating-related attitudes (e.g., dietary restraint, food preoccupation, concern with weight: Beumont et al., 1997; Goldstein, Wilson, Thompson, Potvin, & Rampey, 1995; Romano, Halmi, Sarkar, Koke, & Lee, 2002). With regard to the effect of fluoxetine on treating anxiety and depression in bulimia nervosa patients, the results have been mixed, with some studies reporting a beneficial effect and others not (Beumont et al., 1997; Goldstein et al., 1995; Romano et al., 2002).

**Psychosocial interventions**—A variety of psychosocial interventions have been used for treating bulimia nervosa, and some of these approaches include a form of CBT tailored specifically for the treatment of bulimia nervosa (CBT–bulimia nervosa), IPT, nutritional counseling, and dialectical–behavioral therapy (DBT). To date, CBT–bulimia nervosa has shown the greatest clinical utility in reducing many of the core features associated with bulimia nervosa, including binge eating, purging, dietary restraint, and other eating-attitude-related changes (Agras et al., 2000; Bailer et al., 2004; Bulik, Sullivan, Carter, McIntosh, & Joyce, 1998; Wilson & Shafran, 2005). Other studies examining the combination of CBT and medications, such as fluoxetine and desipramine, suggest that combined interventions may confer an additive benefit (Agras et al., 1992; Walsh, Fairburn, Mickley, Sysko, & Parides, 2004). Unlike in the case of anorexia nervosa, either CBT–bulimia nervosa alone or CBT–bulimia nervosa combined with pharmacotherapy may be considered a relatively effective first-line treatment for bulimia nervosa. Nonetheless, many individuals diagnosed with bulimia nervosa do not respond to these treatments, thus indicating a clear need to develop novel interventions for those individuals who do not respond to the more customary treatments. Most of the research areas highlighted in Table 1—including developing or adapting treatments for adults afflicted with bulimia nervosa to adolescents, clarifying diagnostic issues related to bulimia nervosa and other eating disorders, and assessing the effectiveness of standard treatments in more routine clinical treatment settings—are needed.

**Eating Disorder Not Otherwise Specified**

In the current DSM–IV (American Psychiatric Association, 1994) classification system, individuals with clinically significant disturbances in eating behavior but who do not meet the criteria for anorexia nervosa or bulimia nervosa fall under the category of eating disorder not otherwise specified. This broad diagnostic category comprises six different presentations of eating disorders (American Psychiatric Association, 1994), and clinical reports indicate that the majority of individuals seeking treatment for an eating disorder fall into the eating disorder not otherwise specified category (Fairburn & Walsh, 2002). There are a number of problems with this state of affairs. These problems include, in part, that a diagnosis of subsyndromal anorexia nervosa or bulimia nervosa falling under the eating disorder not otherwise specified category generally communicates very little useful information regarding the severity of the illness or the extent to which subsyndromal anorexia nervosa or bulimia nervosa patients approximate full-syndromal patients in their accompanying clinical features and treatment responses. Clearly, one area in which further research is needed is the diagnostics and classification of the eating disorder not otherwise specified category. That said, the eating disorder not otherwise specified category that is probably the best categorized, has received the most research attention, and is the focus of the remainder of this section of the article is binge-eating disorder.

**Pharmacological interventions**—Medications used for binge-eating disorder have included, in part, antidepressant medications, appetite suppressants, and anticonvulsant...
medications. The most extensively studied pharmacological interventions to date are the SSRIs fluoxetine and fluvoxamine, both of which have been reported to reduce the frequency of binge eating and depression, improve eating-related psychological impairments, and reduce either body weight or body-weight gain (Arnold et al., 2002; Hudson et al., 1998). However, in one study, fluvoxamine was reported to be no more effective than placebo in reducing the number of binge episodes, depression, shape and weight concerns, or body weight (Pearlstein et al., 2003). This result may have been partially a result of the high placebo response found in this study. In another study, fluoxetine and CBT were reported to be more effective in reducing binge eating, depression, and other psychological features associated with binge-eating disorder compared with fluoxetine alone, but there were no differences in weight loss between the treatment groups (Grilo, Masheb, & Wilson, 2005). In other studies, McElroy and colleagues reported that the SSRIs sertraline (McElroy et al., 2000) and citalopram (McElroy et al., 2003) were effective in reducing binge episodes and body weight, but the results were mixed regarding the drugs’ effects on depression. Similarly, the appetite suppressant sibutramine has been reported to significantly reduce the frequency of binge eating, weight loss, and self-reported depression (Appolinario et al., 2003), and the anticonvulsant medication topiramate reduced binge eating and body weight but had no effect on reducing depression (McElroy et al., 2003).

Although a number of the medications described above appear to hold promise for the treatment of binge-eating disorder, there are still a number of issues that need to be resolved before reliable conclusions can be drawn regarding their effectiveness. First, there have been very few rigorous studies assessing the effects of medications on binge-eating disorder, and most of the studies that have been conducted have limited long-term outcome data. This is especially problematic within the context of binge-eating disorder because individuals afflicted with this disorder often improve in response to almost any intervention in the short term.

Psychosocial interventions—Some of the most commonly used psychotherapeutic approaches for treating binge-eating disorder include CBT, IPT, DBT, and self-management strategies. CBT, administered in either individual or group formats, has been shown to be effective in reducing binge-eating episodes, psychological features associated with binge-eating disorder (dietary restraint, disinhibition, negative body image, etc.), and depression in the short term but does not appear to be effective for producing weight loss or preventing weight gain in overweight or obese individuals diagnosed with binge-eating disorder (Hilbert & Tüschen-Caffier, 2004; Wilfey et al., 2002). In studies comparing CBT and IPT, the results indicate that both treatments may be effective in reducing binge eating, depression, and psychological features associated with binge-eating disorder, but neither treatment has resulted in significant weight loss (Wilfey et al., 2002). DBT in the short term has also been reported to produce significant reductions in binge eating, depression, and psychological features of binge-eating disorder but had no significant impact on body weight (Telch, Agras, & Lineham, 2001). One issue that needs to be addressed within the context of behavioral interventions for binge-eating disorder is the relative lack of specificity that many of the psychotherapeutic approaches have for treating the psychological parameters they were originally designed to target. For example, in the studies comparing CBT and IPT, patients experienced improvements in psychological parameters that are not targeted by these interventions. Thus, comparing the more common psychotherapeutic interventions with appropriate control comparison groups (e.g., wait-list controls) will be important. In addition, there has been scant long-term follow-up to the treatments described above, so very little is known about the long-term efficacy of many of the behavioral interventions tested. The research areas outlined in Table 1 are also relevant to binge-eating disorder. Finally, for a recent comprehensive review on anorexia nervosa, bulimia nervosa, and binge-eating disorder, see Berkman et al. (2006).
Looking Forward: Pathways to the Pathophysiology of the Eating Disorders

At present, nearly all of the therapeutic approaches for treating eating disorders have been borrowed from the treatment of other disorders. In addition to factors noted above, a major impediment to developing novel treatments for eating disorders is the lack of a clear understanding of their underlying pathophysiology. Although pathophysiology has been fundamental to the science of cancer, heart disease, and endocrine disorders, the science of mental illness has largely been preoccupied with diagnosis, the development of theories based on observations of behavior, and the promotion of treatments suggested by case reports. This picture is changing with the increasing recognition that mental illnesses are brain disorders (Insel & Quirion, 2005). Unlike neurological disorders with focal lesions, mental disorders appear to involve abnormal activity in brain systems. One implication of this recognition of mental disorders as brain disorders is that the pathophysiology of mental illnesses, including eating disorders, can be approached with the tools of modern neuroscience as well as the behavioral and observational tools of psychology.

To be more truly explanatory, pathophysiology will need to be approached at many levels, from genes to behavior (see Table 2). Over the past decade, there has been a revolution in researchers’ ability to understand the molecular, cellular, and neural-systems bases of several complex behaviors, including feeding, fear, and circadian rhythms. For normative feeding alone, neuroscientists have uncovered several neurochemical systems involved in appetite, satiation, and normative caloric balance (Berthoud, 2002;Horvath, Diano, & Tschop, 2004). Thus far, research has been less successful in identifying the neural bases for any mental illnesses, including eating disorders. But that may soon change with the increasing translation of basic science tools to clinical problems. Below is a summary of just a few of the opportunities at the levels of genes, cells, systems, and behavior. There have been few revolutions in science to match the current revolution in genomics. Following the publication of the human genome sequence in 2003, the human haplotype map, which is a map of common variations in the human genome, was published in 2005 (Altshuler et al., 2005). Although there are roughly 10 million common variations in the human genome, many of these covary in clusters called haplotypes. As a result, much of the variance can be assessed by assaying the haplotypes rather than counting each of the 10 million common variants. High-throughput genotyping chips for these common variants are now available. This means that the association of variations in DNA (genotype) with disease (phenotype) can routinely be tested faster, better, and more cheaply than anyone would have imagined even two years ago.

Will a gene be found for anorexia nervosa, bulimia nervosa, or binge-eating disorder? Probably there will not be a specific gene for any of the major mental illnesses; but it is likely that there will be variations in DNA that are associated with risk. These DNA variants may be common, and they may not code for disease. It is more likely that they will bias for a specific temperament, such as risk aversion or perfectionism, which will in turn be associated with an eating disorder. On the basis of experience thus far in macular degeneration, diabetes, and Crohn’s disease, it might be predicted that the genes involved will be ones that no one has yet studied. Only a small fraction of the more than 20,000 genes in the genome have been investigated; this means that the present is still the discovery phase of genomics. The next five years will be an extraordinary period when, for the first time, the major genomic candidates for normal and abnormal behavior will begin to be discovered.

How will finding genetic variations associated with the eating disorders help define pathophysiology? Genes do not code for behavior; they code for messenger RNAs (mRNAs), which in turn code for proteins, which are the building blocks of cells. Understanding how a specific genetic variation influences function at the cellular level is the next stage. This will be more complicated than identifying genetic variations because each gene may code for
several different proteins, and each protein is part of a complex network of intracellular pathways. This complexity notwithstanding, the tools now exist for identifying thousands of mRNAs and proteins within individual cells. These tools have already helped researchers to understand that the neuroanatomy of the 20th century will not suffice for the 21st century. As just one example, the axiom of “one neuron, one neurotransmitter” has long since been replaced by the insight that each neuron may express thousands of proteins and scores of neurotransmitters. Indeed, many of the most fundamental assumptions about how neurons work have recently been called into question (Bullock et al., 2005). An understanding of the pathophysiology of anorexia nervosa, bulimia nervosa, and binge-eating disorder that starts with identification of genomic variation will need to include an understanding of how this variation alters protein expression in specific cells. Most important, it should be expected that this variation will be manifested through development by altering how neurons mature and connect to form functional circuits.

The third level of analysis involves an understanding of altered systems in the brain. Although most neurological illnesses, such as Parkinson’s disease and Huntington’s disease, involve focal lesions, mental illnesses may be thought of as distributed across neural systems. Neuroimaging has already proven useful for identifying abnormal activity in circuits for cognition and emotion in schizophrenia (Meyer-Lindenberg et al., 2005), obsessive-compulsive disorder (Fitzgerald et al., 2005), and depression (Pezawas et al., 2005). One might expect that functional imaging will also detect altered activity in eating disorders. For example, the interpretation of changes in regional glucose metabolism or hemodynamic signals in the brains of people with anorexia nervosa may be confounded by nutritional effects, but alterations can be detected in weight-recovered patients, including alterations in binding of specific receptor ligands (Kaye, Bailer, Frank, & Henry, 2005). The value of neuroimaging lies not only in the identification of neural systems involved in disorders but also in the opportunity to understand how information is processed in patients with eating disorders, irrespective of their nutritional state.

Finally, the most challenging level of analysis is the study of behavior. Although the last decade has seen the development of revolutionary technologies for genomics, cell biology, and neuroimaging, the analysis of behavior remains the least technical and most skilled level of study. Understanding the eating disorder “phenome” remains a considerable challenge. For example, are there several forms of anorexia nervosa? Can prognosis be predicted? Can risk for anorexia nervosa prior to weight loss be detected? Even defining the core pathology remains controversial. Is this primarily a disorder of body image, self-esteem, obsessive thoughts, or compulsive behavior? Clearly, there is a need to understand the behavioral aspects of this disorder if sense is to be made of the genomic, cellular, and systems data. But it is also worth considering that genetics or neuroimaging may help to detect subtypes of the disorder not evident from the observation of behavior.

Recently, the first studies tracing specific genomic variations through altered cellular activity to abnormal activity in a neural system have been reported (Egan et al., 2003). Although this multilevel approach to pathophysiology is now possible in cancer, researchers have not reached this integrative understanding of any mental illness. As shown in Table 2, the tools to address these illnesses, including eating disorders, now exist; however, it is important to recognize that the aforementioned illnesses will be more complex than most other medical illnesses in that many genes will be involved, there may be no discrete cellular lesion, and the abnormal activity in neural systems could be subtle. Nevertheless, the potential payoff is huge. Genetics can reveal risk, medications and biomarkers can be developed on the basis of identified protein pathways, and imaging may provide clues for treatment response. Although this may seem far-fetched for anorexia nervosa, bulimia nervosa, or binge-eating disorder, recall that these are precisely the tools now in use in the rest of medicine to determine risk for breast cancer.
(genetics, cell phenotyping, and breast imaging) and coronary artery disease (plasma lipids and cardiac imaging). Considering eating disorders as medical illnesses with pathophysologies that can be elucidated with the modern tools of genomics and neuroscience offers the best hope for finding cures or preventive strategies.

Conclusion

The mission of NIMH is to reduce the public health burden of mental and behavioral disorders through research. Eating disorders represent a significant fraction of this burden, although the exact morbidity and mortality attributable to these disorders has been difficult to establish. Although eating disorders are presumably brain disorders, very little is known about their pathophysiology. This may change with the translation of genomic and neuroscience research to the study of these disorders. In addition to a better understanding of the biology of these disorders, specific treatments are needed that can be shown to reliably reduce the symptoms in randomized, controlled trials. Because these illnesses frequently begin in adolescence, there is a need for evidence-based treatments in this age group as well as in adults. Ultimately, the challenge for the treatment of these disorders is the same as with all mental disorders: developing individualized or personalized care that is based on an understanding of what treatment will be most effective in which patient.

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Table 1
Key Areas of Research Needed for Developing and Improving the Treatment of Eating Disorders

Studies designed to test developmentally informed interventions for children and adolescents as well as studies that focus on specialized strategies for understudies groups such as ethnic and racial minorities and men.

Research focused on developing more effective relapse-prevention procedures and maintenance booster therapies.

Identification of new treatment targets that are derived from studies that focus on premorbid traits and traits that persist through the illness and after recovery.

Research that will allow for more precise distinctions within and among the various eating disorders; empirically driven definitions of the terms remission, relapse, and recovery; and how the current nosology captures these definitions over time.

Investigations assessing multimodal interventions in inpatient, outpatient, or partial-hospitalization settings as well as investigations incorporating alternate systems of delivery and therapeutic approaches (e.g., schools, nutritionists, general practitioners, psychologists, psychiatrists) alone or in combination.
### Table 2

**Pathways to Pathophysiology**

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<tr>
<th>Level of Analysis</th>
<th>Genes</th>
<th>Cells</th>
<th>Systems</th>
<th>Behavior</th>
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<tr>
<td>Revolutionary Technology</td>
<td>HapMap, High-speed genotyping</td>
<td>mRNA profiling, proteomics</td>
<td>Neuroimaging, Transgenics</td>
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<td>Level of Inference</td>
<td>Individual variation</td>
<td>Developmental pathways of disease</td>
<td>Altered information processing</td>
<td>Subjective and objective experience</td>
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<td>Relevance to Pathophysiology</td>
<td>Risk vs. resilience</td>
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