Ethics of Communicating Scientific Findings of Autism Risk

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Case Study: The Legacy of Blame in Autism Risk Communication

There remains, despite myriad claims to the contrary, no known etiology for autism spectrum disorders (ASD). From blaming mothers to genes to vaccines and vaccine ingredients, the search for what causes ASDs has produced more condemnation and controversy than a definitive understanding of the group of developmental disorders under the ASD umbrella. Only recently, through the relentless efforts of parent advocacy groups working with scientists and other interested stakeholders, has the National Institutes of Health dedicated significant resources to the study of ASD etiology.

Once diagnosed as childhood schizophrenia and a host of other neuro-psychiatric disorders, autism was first named by the psychiatrist Leo Kanner in 1943 as a disorder of "disturbances of affective contact." Kanner, a founder of the field of child psychiatry and its director at the Johns Hopkins Hospital, first described the etiology of autism as being biologically hereditary in nature. "We must, then, assume," Kanner wrote in his landmark paper in the Journal *Nervous Child*, "that these children have come into the world with innate inability to form the usual, biologically provided affective contact with people, just as other children come into the world with innate physical or intellectual handicaps" (Kanner, 1943).

But before the end of the 1940s Kanner abandoned a biological explanation for the disorder for a purely psychogenic one. Kanner's new description of autism etiology laid blame squarely on bad parenting. Parents of autistic children "lacked the warmth which the[ir] babies needed." "Maternal lack of genuine warmth," Kanner observed in autistic mothers "is often conspicuous in the first visit to the clinic," while fathers of autistic children related to their children with "unemotional objectivity." The children of these parents were "exposed from the beginning to parental coldness, obsessiveness, and a mechanical type of attention to material needs only." And thus from Kanner was born what would become one of the most destructive and reviled theories of autism etiology—the refrigerator parent or, more commonly, mother. In Kanner's view, autistic children were "kept neatly in refrigerators that did not defrost. Their withdrawal seems to be an act of turning away from such a situation to seek comfort in solitude" (Kanner, 1949).

If Leo Kanner was the founder of the field of autism studies and the first scientist to offer a theory of both the nature and etiology of autism, then the famed University of Chicago psychologist Bruno Bettelheim quickly became, in both scientific and popular circles, the field's chief spokesperson and researcher. Although other scientists produced research echoing Kanner's bad parenting hypothesis, including the Nobel laureate Nikolaas Tinbergen and the psychologist Harry Harlow, Bettelheim's mark on autism research remains unparalleled. From his perch as the Director of the Sonia Shankman Orthogenic School at the University of Chicago, Bettelheim's work was embraced, for most of his career, by the public and by the academy.

Bettelheim's most prodigious work on autism, *The Empty Fortress: Infantile Autism and the Birth of the Self* (1967), was a psychoanalytic rendering of the causes of autism. Based on a series of

case histories from his work at The Orthogenic School, Bettelheim locates *The Empty Fortress* squarely in science, not speculation, writing that "the contents of this volume do not derive from introspection. They are based on the findings of trained observers, their observations checked against each other, and on inferences drawn on that basis" (Bettelheim, 1967; p.8). For Bettelheim, autism emerges in purely psychogenic terms: there is a failure between parent and child to form normal social relations during the first two years of life. Bettelheim delineates three critical stages during which this occurs: in the first stage, children recognized as autistic during the first six months of life have failed to "form social relations because they have been too sorely disappointed in the world;" in the second stage, children diagnosed during months six to nine who have tried to "relate to the other but finds him unresponsive… may give up trying to relate." Moreover, by "not having found the other, he cannot find the self either"; and, finally, according to Bettelheim it is during third stage, from eighteen months to two years, when "autism is most commonly recognized." This "is the age when the child can approach or avoid contact with the world not just emotionally, but by walking away from it all" (Bettelheim, 1967; pp.46-7).

In an early chapter of the book, in what can be interpreted as an act either of intellectual dishonesty or self-deception, Bettelheim sought to distance himself from blaming mothers for their child's diagnosis. He argued that the mother neither "creates the autistic process, nor that specifics of her pathology explain those of her child." Instead, he suggested that "it is not the maternal attitude that produces autism, but the child's spontaneous reaction to it." Bettelheim wrote:

> *Thus the child's initial autistic reaction can be brought about by a variety of conditions, but whether this temporary reaction becomes a chronic disease depends on the environment's response. Nevertheless, both the original reaction and the later autistic behavior are spontaneous and autonomous responses on the part of the child. (p.70)*

Despite Bettelheim's protestations otherwise, in his formulation of autism etiology, only the mother or father could be blamed for the onset of autism.

The Empty Fortress was reviewed widely in the popular and academic press. The *New York Times Book Review* called Bettelheim's work "a passionate, lucid account of these children who have become empty centers surrounded by an impenetrable wall of symptoms." Of Bettelheim, the reviewer wrote that "no brief review can do justice to his wisdom or his compassion." The reviewer also insisted that Bettelheim did not blame autism etiology on parents and thus "points no accusing finger" (*NYTimes,* 1967). In *The New Yorker* the historian Peter Gay called Bettelheim "a hero," and insisted that those working with him at the Orthogenic School were "magnificent." According to Gay, Bettelheim's "theory of infantile autism is in all respects much superior to its rivals" (Gay, 1968). The academic reviews were no less laudatory. Writing in *Contemporary Psychology* Nicolas Hobbes called the book "a work of great beauty, warmed by compassion, informed by years of experience," and concured with Bettelheim's conclusion that "autism is the child's radical defense against the mother's desire that he not exist." Hobbes did acknowledge, however, that Bettelheim "seems inappropriately and implacably hostile" to the parents of autistic children (Hobbes, 1968).

The coddling reviews and darling media attention given to Bettelheim and *The Empty Fortress* were met with resistance by some parents and scientists. Bernard Rimland, a parent of an autistic son and a research psychologist with the U.S. Naval Personnel Research Laboratory,

published *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior* in 1964. The book rejected a psychogenic theory of autism etiology in favor of a biological explanation. Rimland concluded that autism was an inborn condition that accompanied children from birth (Rimland, 1964). In a letter in the *New York Times* soon after the publication of *The Empty Fortress*, Rimland called Bettelheim's theory "totally unsupported speculation," and concluded that "to heap guilt, based on disproven, circumstantial evidence, on these parents is an act of irresponsibly cruelty" (*NYTimes,* 1967). Even Leo Kanner, who had coined the term refrigerator parent, had by the late 1960s, returned to his original theory that autism was a biological condition. At a meeting of parents of autistic children in 1969, Kanner seemed to recant his blame theory, telling them, "in no uncertain terms" that the condition was "innate" (Dolnick, 1998).

Issues To Consider:

- What role does this legacy of blame play in contemporary debates about autism etiology?

- The rejection of the refrigerator parent hypothesis in its various forms took time. Biological and environmental theories of autism etiology did not become the dominant approach in research for at least a decade following the publication of *The Empty Fortress*. What do you think accounts for the shift? Were these changes a shift in scientific thought? What role do you think parents played in shifting the nature of autism etiology research? And what role did they play in changing the nature of autism risk communication?

- The vast majority of reviews in the psychological and popular literature were admiring, almost sycophantic of Bettelheim and his work. What do you think accounts for this? Do we live in a similar research environment today?

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Case Study: Genome Wide Association Studies (GWAS) and Autism: Issues for Risk Communication and Ethics

GWAS Background

Genome wide association studies, or GWAS, are a new technology helping scientists scan large areas of the human genome and search for genetic variants associated with human disease. Utilizing novel bioinformatics and high-throughput genotyping technologies, GWAS can aid geneticists as they search the human genome for a gene or genes associated with a particular disease. GWAS has already been used to study a wide-range of human disease traits, and has aided in advances in cardiology, infectious disease, oncology, neurology, and psychiatric disorders (Psychiatric GWAS Consortium Steering Committee, 2009).

GWAS works by comparing hundreds of thousands or even millions of genetic variants in the human genome known as single nucleotide polymorphisms, or SNPs, in two sets of samples—one with a particular disease and one without—and uses this comparison to see if any of these variants relate to a specific disease or health-related trait. Methods are also available to perform GWAS analyses in family based samples (the simplest being 'trios' – affected individuals and both biologic parents). GWAS approaches are designed to detect association of a disease with common polymorphisms (where at least 5% of the population has the variant that increases disease risk). This technique is made possible by the more than 17 million human SNPs that have already been identified and catalogued in the National Center for Biotechnology Information's SNP database (Pearson & Manolio, 2008). The GWAS approach can also be used to search for structural variants in the genome – the most common of these being copy number variations (CNVs), which are segments of DNA sequence that contain repeats or deletions of nucleic acids. Structural variation in DNA has long been known to cause disease, but this was thought to only occur in very rare genetic conditions or in rare forms of more common conditions (e.g., certain obvious structural DNA variation has been linked to autism for years, but these particular variations are believed to account for a very small proportion of autism cases). However, CNVs have now also been found to occur commonly in the genome – even in the genomes of healthy individuals - forcing scientists to consider the nature of this variation and ask if CNVs are harmless variation or an indication of disease risk?

GWAS and Autism

GWAS may be a useful tool in the attempt to understand the genetic mechanisms underlying autism spectrum disorders (ASDs). GWAS autism studies survey and compare the entire genome of both individuals with ASD and controls, aiming to identify genetic discrepancies between the two groups (Chen, Jorgenson & Cheung, 2009). Given that genome-wide approaches are relatively new technologies, it is not surprising that to date, there have been only three published autism GWAS studies focused on SNPs and five genome-wide autism studies focused on CNVs. In comparison, according to the HuGE navigator database, Phenopedia, maintained by the Office of Public Health Genomics at the Centers for Disease Control in Atlanta (CDC), there are 19 GWAS analyses of schizophrenia and 12 published

GWAS analyses for "Type 1 diabetes." More genome-wide studies in autism are sure to be emerging in the near future.

Several recent GWAS studies have identified candidate genes that may be associated with ASD. For example, two recent papers have identified that common genetic variants on 5p14.1 may indicate susceptibility to ASDs (Wang et al., 2009 & Ma et al., 2009). One of these studies identified several genes that were associated with increased risk for autism, but the study's most significant findings were six SNPs located between two genes CDH10 and CDH9 on chromosome five. The authors of the study hypothesize that these SNPs "regulate the expression and action of either CDH10 and CDH 9" (Wang et al., 2009; p.531). Because both of these genes are believed to play an important role in fetal brain development and function—playing a role in neuronal cell-adhesion—the study's authors suggest that "variants in this gene class may be involved in shaping the physical structure and functional connectivity of the brain that leads to the clinical manifestations of ASDs" (Wang et al., 2009). However, while each GWAS study reveals important etiological clues about ASD, the complex phenotype of ASD creates significant obstacles in establishing causality. In print, the Wang et al article concurs with this assessment, writing that their study, "together with studies addressing epigenetic modifications and comprehensive analysis of environmental risk factors… can be better integrated to improve our understanding of the molecular basis of ASDs, and foster the development of early preventive and corrective treatment" (Wang et al., 2009).

GWAS in the media

The release of Wang's findings was accompanied by substantive media coverage and provides an opportunity to discuss the role that both scientists and journalists play in risk communication through the media. First, a BBC News Online story, published the day the Wang study was released, argued that "scientists have produced the most compelling evidence to date that genetics play a key role in autism." The BBC article also claimed that if one common genetic variant identified in the study were corrected, it "would cut cases of autism by 15%" (BBC News Online, 2009). The original Wang et al. scientific publication *does not* directly make this claim and no authors are quoted in this report supporting the figure. The source most likely was the press release issued by the sponsoring institution which said in its opening paragraph that the study "…pinpoints a gene region that may account for as many as 15 percent of autism cases…" It is unclear how this estimate was derived and, consequently, it raises real questions about whether or not and how this percentage should be reported.

In a Los Angeles Times article published soon after the study's release, one of the lead investigators is quoted as saying that the work of his team "opens up the opportunity someday for new interventions to fix the bad consequences this variant has on brain function and development" (Tsouderos, 2009). Similarly, a Bloomberg News article quotes an author as saying the GWAS results "gives scientists targets to perhaps begin developing treatments" (Lopatto, 2009). Although both authors' quotes are caveated and clearly forward looking, they do call attention to treatment implications of these very preliminary and un-validated findings. Researchers are often asked directly by journalists to comment on the direct implications early work might have on patients and their families and scientists typically are genuinely hopefully that new findings will impact on treatment or prevention strategies and will, someday, directly benefit patients and families.

However, ASD is a complex phenotype likely to have several contributing genetic components, and it is worth considering whether quotes like these exaggerate the clinical significance of GWAS findings, giving false hope that full understanding of ASD etiology and treatment will come shortly after the publication of these studies (Tabor and Cho, 2007). Interestingly, the same press release that included the troublesome "15 percent" figure also included, in its last paragraph, the following quote from another study co-author, "Although we cannot immediately apply this research to clinical treatments, these findings increase our understanding of how autism spectrum disorders arise, and may in time foster the development of strategies for prevention and early treatment." This quote includes some of the same forward-looking optimism for eventual treatment implications as the others, but begins by clearly stating that the results are not immediately applicable in clinical settings. Realistically, scientists are a long way from deciphering the complex etiology of ASD. As noted in the paper's "Discussion," a full etiological understanding of ASD will likely come from a pooling of research from a myriad of scientific fields (genomics, epidemiology, neuroscience, etc.).

Challenges for the Communication of GWAS Findings

GWAS is a new technology and as such, there is little knowledge of the public's general understanding of the technology, or of the technology's impact on the public's understanding of autism etiology. The technology utilized in GWAS research is innovative and complex, making dissemination of findings even more difficult than communicating basic genetics (McMahon, Baty & Botkin, 2006). Further, it is an approach that does not build on specific evidence or test a specific hypothesis beyond sucpicion of genetic suceptibility. Consequently, while replication is critical to all scientific findings, replication is especially important in GWAS. Initial recommendations on replication have been made (Chanock et al, Nature, 2007) and are generally being followed. However, the scientific community is still discussing further standardization of GWAS results reporting (Johnson and O'Donell BMC Medical Genetics, 2009). No matter how this develops, GWAS publications are likely to be more multi-layered than other types of research reports, potentially including – initial findings, replications, reports on gene expression and/or function, etc. For example, Wang et al include replication findings as well as new findings on expression of CDH and CDH10 in the brain in their initial GWAS report. This makes for an even more complex grouping of findings for audiences to evaluate, synthesize, and communicate. At the same time, the totality of the findings in any one report should still, in virtually all cases, be considered preliminary, unlikely to directly influence prevention or treatment strategies in the near term. Additional studies of a different design will be needed to determine if identified genetic variants have diagnostic utility, and, on top of that, additional studies of yet another design will then be needed to determine if these genetic variants have any utility in clinical genetic testing (Tabor and Cho, 2007).

Issues to Consider:

- There is often some discrepancy in emphasis between the information presented in scientific journal articles and the information presented in popular media – particularly with respect to direct and immediate benefit to patients and families. How can science journalists, scientists, and institutional public relations offices work together to ensure an accurate portrayal of GWAS information? Is there a way for scientists to discuss the potential significance of their findings and speculate on their eventual clinical applicability,

without claims for their potential future use becoming the centerpiece of media accounts of research findings?

- Does media coverage of GWAS studies encourage a view that autism is ultimately a genetic condition? Is this appropriate? Are there effective ways to communicate what may be more complex realities?

- How can pediatricians, genetic counselors, and other autism experts help families understand differences between early-stage genetic discovery research and findings that have clinical significance? What are the approaches that should be taken when families and clinicians or researchers have different views on the level of evidence needed to prompt a clinical decision?

- Novel findings, by nature, attract media attention (novelty is the definition of "news"). Should we be thinking of ways to make studies that replicate findings and/or summary reports that synthesize multiple findings more newsworthy and more accessible to clinicians and families?

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Case Study: Television, Rainfall, and Autism

In late 2006, Cornell University issued a press release (1) entitled "Early childhood TV viewing may trigger autism, data analysis suggests." The release was triggered by a forthcoming presentation at an economics conference of a project led by a professor of management and business from Cornell's nationally ranked business school. The release claimed that the research "…suggest[s] a connection between early childhood television viewing and the onset of autism," and went on to say:

> *We tested our hypothesis using existing, well-known data. The analysis shows that early childhood television viewing could be an environmental trigger for the onset of autism and strongly points to the need for more research by experts in the field of autism.*

The release explained that the analysis did not directly test the association between TV viewing and autism risk but explored the county-level connections between autism and factors related to the amount of TV watched - precipitation and cable TV subscription prevalence. At the close of the release, a co-author was quoted as saying:

> *Our analysis is not definitive, but it certainly raises questions that seem to have gone unasked in autism research to date. The medical community is increasingly convinced that something is happening in the environment that triggers an underlying biological or genetic predisposition toward autism, and these findings strongly support the need for taking a closer look at early childhood television viewing.*

The lead author posted the full 2006-version of the paper, entitled "Does Television Cause Autism," on his personal website, where it remains (2).

The press release generated a significant amount of media attention at the time. Some of the coverage simply reported back and amplified the information in the release. A WebMD report (3) that was posted to other news websites, including cbsnews.com, contained the following:

> *[The author] asked his colleagues in the medical world to look at the issue. Nobody would. So he assembled a research team and did the study himself – using tools more often seen in economic studies than in medical studies. The results bolstered his suspicions. "'We are not claiming that we have definitive evidence. But we have evidence that is awfully suggestive of a link between TV watching and autism…"*

Others in the media took a more critical stance. *Time* magazine published an article (4) commenting, "The as yet unpublished Cornell University study…is constructed from an analysis of reported autism cases, cable TV subscription data and weather reports. Yes, weather reports.

And yet, it all makes some kind of sense in the realm of statistics." The *Time* article went on to note that the authors "…turned instead to what most scientists would consider wildly indirect measures: cable subscription data (reasoning that as more houses were wired for cable, more young kids were watching) and rainfall patterns (other research has correlated TV viewing with rainy weather)" and also commented on the paper's use of language suggesting that the TV-autism relationship was one of cause and effect: "How can these researchers suggest causality when no actual TV watching was ever measured?"

The paper suggests causation because they employed a statistical technique called instrumental variables modeling, commonly used in econometrics. In the *Time* magazine piece, the lead author noted, "The standard interpretation of this type of analysis is one of cause and effect." While that has been true to some extent historically in economics, in recent years much attention has been given to the assumptions behind the instrumental variable approach and the fact that this statistical technique, like all others used to evaluate non-experimental data, that come from sources other than randomized trials, can not solve all and lead to pure, unqualified causal inference. A recent commentary (5) on the instrumental variable approach in the journal *Epidemiology* noted that "users of IV methods need to be aware of the limitations of these methods. Otherwise, we risk transforming the methodological dream of avoiding unmeasured confounding into a nightmare of conflicting biased estimates."

In the end, the original paper built around the TV viewing hypothesis did not appear in the peer-reviewed literature. However, in 2008 a revised and re-titled version of this work was published in the *Archives of Pediatric and Adolescent Medicine* (6). The paper, now titled "Autism prevalence and precipitation rates in California, Oregon, and Washington counties," did not include the original instrumental variable analyses and dropped consideration of cable television subscription data altogether. Instead it used more standard statistical methods to correlate precipitation and autism prevalence data, both collected at the county level. (In epidemiology this is known as an ecologic analysis – an analytic approach that can generate hypotheses but, on its own, generates weak evidence toward proving causation.) In the Discussion section, the paper mentions a series of factors potentially associated with precipitation, including television viewing, but also including low vitamin D levels and higher exposure to indoor chemicals. The paper adopts as its motivating position the overarching, and more widely accepted idea, that autism is caused by an environmental trigger among genetically susceptible children. On one hand, the paper suggests that the correlation of county-level data generates "empirical evidence" supporting this general mechanism, though on the other hand it recognizes that it does not approach any kind of direct test of an association between specific environmental exposures and autism risk. The following is the paper's concluding paragraph:

> *Because we do not provide direct clinical evidence of an environmental trigger for autism among genetically vulnerable children that is positively associated with precipitation, our results are clearly not definitive evidence in favor of the hypothesis. But the results are consistent with the hypothesis, and, therefore, further research focused on establishing whether such a trigger exists and on identifying it is warranted.*

Cornell University's Johnson School posted on its Newsroom website an announcement of the publication of this paper (7) under the headline, "AMA journal publishes study showing evidence of a major environmental trigger for autism." The announcement included the following quote from the lead author:

> *This analysis is an important first step towards identifying a specific environmental trigger, or triggers, for autism. Our hope is that this study will spur those in the medical community to investigate what the specific trigger might be that is driving our findings, so that countless children can be spared an Autism Spectrum Disorder diagnosis.*

The announcement ends by stating the paper "refines previous research on autism conducted by this team. " It continues, saying that this "latest report considers a specific hypothesis – that there exists an important environmental trigger for autism among genetically predisposed children that is positively associated with levels of precipitation – and solidifies the need for further research focused on identifying what the exact environmental trigger might be."

The *Archives of Pediatric and Adolescent Medicine* included with their publication of the paper a commentary by Noel Weiss, a senior leader in epidemiology and former department chair at the University of Washington (8). After briefly noting the major limitations of the ecologic approach used in the paper, Weiss goes on to say that, despite these limitations, he supports the decision to publish the paper. He says:

> *The primary audience for the article…is not the practicing pediatrician, and certainly, it is not a member of the public at large. These individuals cannot take away any practical message from it. Rather, the primary target is an investigator interested in the causes of autism, someone who might be able to test one or more of the etiologic hypotheses that derive from the research… If a study's findings are no more than tentative ones – certainly, th[ese] must be viewed as tentative – responsible authors will stress this, just in case members of the lay public are "eavesdropping" on the exchange of information between scientists. In this instance, I believe that [these authors] have indeed reported their results responsibly. They have made it clear that the message the public should take from their data regarding precipitation and autism is the same one suggested by an editorialist commenting on a recently observed modest association between prenatal exposure to cell phone use and behavior problems in childhood: "No call for alarm, stay tuned."*

Issues to consider:

- The first version of this paper was built around a specific a priori hypothesis –that early television exposure causes autism – while the second, published version, takes a more exploratory approach (despite the fact that the press release accompanying it attempts to portray it as more hypothesis-driven than the initial analysis). How important is an a priori hypothesis to the real and perceived impact a particular research finding has?

- What do you think of Weiss's comment that some communication in the scientific literature is "between scientists" and that the lay public are "eavesdroppers" on these exchanges?

- Does the interesting evolution of this work influence the real or perceived level of evidence provided by the science therein?

- Should scientists and their universities actively seek media coverage of all new findings? If not, how should they decide which findings are or are not worthy of external publicity?

- If, instead of rainfall, this analysis correlated autism prevalence with county-level data on an environmental chemical in drinking water (say, for example, the insecticide methoxychlor, - http://epa.gov/OGWDW/contaminants/basicinformation/methoxychlor.html), and found similar associations, do you think the repercussions of the Archives publication would have been different? Why or why not?

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