

# Children in Clinical Research: A Conflict of Moral Values

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## Abstract

This paper examines the culture, the dynamics and the financial underpinnings that determine how medical research is being conducted on children in the United States. Children have increasingly become the subject of experiments that offer them no potential direct benefit but expose them to risks of harm and pain. A wide range of such experiments will be examined, including a lethal heartburn drug test, the experimental insertion of a pacemaker, an invasive insulin infusion experiment, and a fenfluramine "violence prediction" experiment. Emphasis, however, is given to psychoactive drug tests because of the inherent ethical and diagnostic problems involved in the absence of any objective, verifiable diagnostic tool. Effort is made to provide readers comprehensive reference sources to evidence-based reports about the serious risks these drugs pose for adults and children so that the reader may judge whether the benefits (if any) outweigh the risks for children.

The first ethical issue raised by these experiments is: did the severity of illness in these children justify their exposure to short and long-term risks? The ethics of the experiments will be evaluated by referring to existing codes of medical research ethics—the Nuremberg Code, the Declaration of Helsinki, and the federal Code of Regulations. The thirteen cases presented will demonstrate that children are being used in ever more speculative experiments, often in the absence of a therapeutic intent, but a significant chance for causing harm and / or discomfort. Some of the experiments were designed to explore the mechanisms of pathology and pharmacological interventions, or the response of neurological brain receptors to chemical provocation ("challenge"). Others were designed to test the safety or efficacy of new drugs, even to test these drugs on healthy children who were *hypothesized* to be "at risk." Children and adolescents have been subjected to "forced dose titration" experiments that induced a spectrum of severe adverse effects, including insomnia, extreme restlessness, agitation, (akathisia) and self-injurious behavior. FDA reports show that suicide is a significant issue in psychotropic drug trials—in pediatric trials the problem is even greater. The paper aims to demonstrate how the enactment of the Better Pharmaceuticals for Children Act (incorporated into the Food and Drug Administration Modernization Act, FDAMA), set in motion a radical shift in public policy by providing huge financial incentives to pharmaceutical companies to test new or patented drugs in children.

Federal policy shifted from one aimed at protecting children by setting limits on permissible research risks, to

a policy aimed at broadening the inclusion of children as test subjects. It will be shown how the FDA and the Department of Health and Human Services lifted regulatory restrictions to permit research involving greater than minimal risk to be conducted on healthy children, claiming that all children are potentially "at risk" of a future condition. Children were in this way deprived of regulatory protections. An argument will be made that the approval of nontherapeutic, harmful experiments—such as exposure of toddlers to lead poison—under the current gate keeping system raises serious doubts about the sustainability of institutional review boards (IRBs) as protectors of human research subjects. Children, who are precluded from exercising the adult human's right to informed consent, are being exploited as commodities for commercial ends. It is the position of the author that nothing less than the enactment of a federal law mandating a radical overhaul of the current research review system, with independent checks and balances, will provide children the legal protections they need. Ten specific recommendations are offered to protect children from harmful experiments.

## Introduction

The aim of this paper is to examine the culture in which biomedical research is conducted in the United States; and to describe in detail a wide range of harmful experiments to which children have been subjected. None of the experiments described served the children's best interest. The examples that will be discussed include: a lethal heartburn drug [Case 3], the questionable insertion of a pacemaker [Case 2], and various psychoactive drug trials—including stimulants, antidepressants and antipsychotics—that have been (and are increasingly) tested in and experimentally prescribed for children. Three examples of wholly non-therapeutic research will also be discussed—healthy children were exposed to fenfluramine, a neurotoxic drug, in a "violence prediction" experiment [case 11]; to an invasive insulin infusion experiment [case 1]; and toddlers exposed to lead poison in a lead abatement study [case 9]. Emphasis in this paper is given to psychoactive drug tests in children because of the inherent ethical and diagnostic problems involved, and the severe side effects that have been linked to these drugs—including their potential to cause long-term neurological, physical, and cognitive harm. It will be argued that children are in great demand for testing these drugs for commercial interests. In the cases described the children who served as subjects did not suffer from life-threatening conditions requiring such invasive, high-risk interventions. Thus, it cannot be argued that the potential benefit outweighed the risks and

discomfort.

The first ethical issue raised by these experiments is: did the severity of illness in these children justify their exposure to both short and long-term risks? The cases raise serious concerns that children who are not sick, that is, who do not meet the criteria of a diagnosable disorder or condition, are increasingly being sought as "risk bearing" subjects to test drugs whose safety is unknown (even in adults), for disorders they may never get. The experiments raise serious moral concerns about whether children are being exploited in drug research as means to an end because they are unable to protect themselves, dependent as they are upon others to make decisions on their behalf. Children are precluded from exercising the human right to informed consent.

### **Research codes of ethics-to whom do they apply?**

The historical record demonstrates that the rights of the individual can be violated, even where codified ethical standards exist to protect those rights. The revelations at the end of World War II, about medical atrocities committed by Nazi doctors on inmates at Auschwitz, demonstrated that neither the Hippocratic Oath ("primum non nocere" "First, do no harm") nor codes of professional ethics had sufficed to deter those doctors from conducting unspeakable medical experiments. An American military tribunal tried 23 leading Nazi doctors at Nuremberg finding them guilty of crimes against humanity. The tribunal's 1947 verdict included a section entitled, "Permissible Medical Experiments"-known as the Nuremberg Code,<sup>1</sup> which is the cornerstone for all subsequent codes of medical research ethics. In 1964, the World Medical Association (WMA) adopted the Declaration of Helsinki,<sup>2</sup> which focuses on research involving ill patients.

However, American medical research ethics were not influenced by these international codes. Medical science burgeoned in post-war America; it was infused with a spirit of adventure, optimism and confidence in the inherent goodness of the scientific endeavor. In 1998, Allen Hornblum observed in his book, *Acres of Skin*: "Rather than embracing the Nuremberg Code, the American medical establishment considered it a 'good code for barbarians,' but an unnecessary code for ordinary physician-scientists."<sup>3</sup> Then and now, many in the medical research community believed the restrictions imposed by these international codes coupled with the Hippocratic principle were too restrictive for physicians who had not committed medical atrocities.

American physicians thus disregarded the ethical restraints in research involving human beings when they were inconvenient. This self-conferred ethical loophole has resulted in a collision between the moral imperative to protect the human subject from harm or exploitation, and the pragmatic, utilitarian ethics of business. But when revelations surfaced in the press about unethical experiments by American researchers,<sup>4</sup> a national commission was convened and its 1979 published recommendations, the Belmont Report,<sup>5</sup> laid down three ethical principles to pro-

tect human subjects: respect for persons; beneficence and justice. However, noncompliance with ethical standards remains a troubling issue in American research. Today, researchers are again being criticized at home and abroad for conducting medical experiments without regard for the rights and welfare of the individual human subjects as mandated in those international and national codes of ethics.<sup>6</sup> What's more, prominent bioethicists such as Dr. Robert Levine<sup>7</sup> of Yale University have taken the moral relativist position to argue against applying Western standards of research universally. According to this view, core moral principles of self-determination, informed consent, and equal treatment would be an option rather than an absolute standard.

A series of reports demonstrating institutional failure to protect human subjects have shaken public trust in the American research establishment.<sup>8</sup> Experiments were conducted, whose design and procedures caused preventable harm and increased suffering, thereby violating the ethical mandate under the Nuremberg Code-"avoid all unnecessary physical and mental suffering;"<sup>9</sup> the Declaration of Helsinki-"the well being of the human subject should take precedence over the interests of science and society;"<sup>10</sup> "the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods;"<sup>11</sup> and the principle of *beneficence* articulated in the Belmont Report -(1) "do not harm" and (2) "maximize possible benefits and minimize possible harms."<sup>5</sup> Children, it will be shown, have been subjected to risks of harm-immediate and long-term, not to mention pain-in experiments that failed to "minimize possible harms." The record demonstrates that the interests of science and commerce had been placed well above the welfare young children in experiments approved by local institutional review boards (IRBs) at prestigious academic research centers. These experiments, and others elucidated elsewhere,<sup>12</sup> had the approval of Government agencies, including the National Institutes of Health (NIH) and Food and Drug Administration (FDA).

In the wake of a stream of public disclosures in recent years about unethical research practices at premier research institutions, some resulting in preventable deaths, led to a perception-acknowledged by the Secretary of Health and Human Services-of a research establishment out of control.<sup>13</sup> At the same time, the U.S. government sent a delegation to the World Medical Association in 2000 to pressure for revisions to the Declaration of Helsinki (DOH).<sup>14</sup> The delegation lobbied to weaken existing ethical standards in order to legitimize unethical practices and to facilitate the interests of research. The delegation's proposals, however, did not represent a consensus in American ethical standards of research. There were other voices, including Dr. Troyen Brennan<sup>15</sup> of Harvard University and Dr. Kenneth Rothman<sup>16</sup> of Boston University and Dr. Karin Michels. They argued against calls to weaken the protection of human subjects, insisting that such calls were motivated by "utilitarian efficiency

aligned with marketplace values."<sup>15</sup> On October 7, 2000, the WMA rejected the proposals for revision, only to vacillate, adding a footnote "clarification" to the placebo paragraph on June 2002.<sup>17</sup>

As the examples described in this paper will make clear, there is a pressing need for an enforceable system of independent checks and balances to protect children from research that undermines their best interests. Children, it will be shown, are being used in ever more speculative experiments, often in the absence of a therapeutic intent, wherein there is significant chance for causing harm and / or discomfort. Some of the experiments were designed to explore the mechanisms of pharmacological interventions, or the response of neurological brain receptors to chemical provocation ("challenge"), or to test the safety of new drugs, or to test these new drugs on healthy children who were *hypothesized* to be "at risk." This paper attempts to show that during the 1990s a radical policy shift was taking shape that lifted regulatory protections for children, culminating in the enactment of the 1997 the Better Pharmaceuticals for Children Act, which was incorporated into the Food and Drug Administration Modernization Act (FDAMA).<sup>18</sup> This legislation provided pharmaceutical companies financial incentives-six months of extended patent protection (market exclusivity) for new or patented drugs that were tested in children. Most commentators, who represent the interests of a consortium of research stakeholders, have focused on the number of drug labeling changes that resulted,<sup>19</sup> but in this paper the focus is on the predictable, if unintended impact the legislation has had on children who in greater numbers have been subjected to the hazards of medical research. The cases that follow demonstrate how extensively the welfare of children has been compromised. To understand why children have become sought after subjects for drug trials one must first examine the culture, the dynamics and the financial underpinnings that determine how biomedical research is conducted.

### **Conflict of interest characterizes the culture of research**

In 1997 the author testified before the National Bioethics Advisory Commission (NBAC) about conflict of interest, betrayal of trust, and the undue influence of the drug industry, citing reports about physicians accepting large payments from drug companies to prescribe their products and refer patients for clinical trials to test the safety and efficacy of new products.<sup>20</sup> In some cases, doctors with academic affiliations have been paid as much as \$30,000 per patient per drug trial.<sup>21</sup> At the time, these issues had not been acknowledged widely in the academic community. Following the testimony, the NBAC chairman, Dr. Harold Shapiro (then President of Princeton), conveniently decided that the commission would not address researchers' financial arrangements, "after all, this is a capitalist country." Dr. Shapiro neglected to mention that he was drawing a salary from Dow Chemical Company, on whose advisory board he sat.<sup>22</sup>

By 2000, however, concern about conflict of interest in academia had reached a critical mass: (then) U.S. Secretary of Health and Human Services, Donna Shalala, convened a conference,<sup>23</sup> and Dr. Marcia Angell, (then) editor of *The New England Journal of Medicine (NEJM)*, learned that the Journal's conflict of interest policy had been breached by several Journal authors and editors who had failed to disclose their financial ties to the companies whose products they had reviewed.<sup>24</sup> Dr. Angell was determined to enforce the policy, but to her dismay, she found out just how "ubiquitous and manifold such financial associations" had become in academia. She could barely find a research psychiatrist who did not have financial ties to industry, to write an unbiased review of antidepressant drugs. Angell wrote a highly critical, influential editorial in the *NEJM*, "Is Academic Medicine for Sale?"

The ties between clinical researchers and industry include not only grant support, but also a host of other financial arrangements. Researchers serve as consultants to companies whose products they are studying... enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies... Many also have equity interest in the companies.<sup>25</sup>

The major concern of critics, such as Angell, is that the "breaching of the boundaries between academic medicine and for-profit industry" is undermining the integrity of science and medicine. We rely on the scientific method of unbiased review of the evidence to ensure the safety and functionality of vital goods and services. If the accuracy and reliability of reported research findings couldn't be trusted there would be no safeguards to prevent harmful medicines from being marketed. Indeed, as will be shown, industry's undue influence in the drug approval process has already resulted in the approval of harmful drugs that were then recalled.

An ineffective system of safeguards coupled with increased financial pressures to cut ethical corners in order to speed up the process, have given rise to unethical conduct and periodic exposes in the press. In 1965, Morton Mintz, the prize winning journalist who reported the thalidomide story, wrote:

...there have been instances when our excessive trust in certain corporate consciences has been rewarded with inadequately and even fraudulently tested drugs, with useless drugs and inferior versions of good drugs, with protraction of illness, and with waste of our money, in order that sales may begin and continue, regardless of whether we are healed and spared pain, evidence of serious and even lethal effects has been withheld from the responsible government agency and concealed from the medical profession and the public.<sup>26</sup>

Since Mintz made that statement, "corporate con-

science" and utilitarian business ethics have further infiltrated academic research and regulatory agencies, further undermining the already inadequate checks and balances needed to protect both patients in clinical care and subjects in research. To gain insight about the factors that led to the erosion of independent checks and balances in the research oversight system, it is instructive to revisit the consequences of laws passed in the 1990s. In 1992, the Prescription Drug User Fee Act (PDUFA)<sup>27</sup> brought industry funding and concomitant industry influence into the FDA drug evaluation and approval process. Both PDUFA and the FDA Modernization Act (FDAMA)<sup>18</sup> had been passed by Congresses under intense pressure from AIDS activists seeking immediate approval of potentially life-saving, experimental drugs. The AIDS epidemic effectively presented the pharmaceutical industry with an opportunity to "loosen regulatory brakes"<sup>28</sup> to speed up the approval process. The FDA applied both laws broadly to permit the fast-track approval process not only for drugs intended for life-threatening conditions such as AIDS, cancer, cardiovascular and liver diseases. FDA sanctioned the testing of drugs intended for minor ailments—such as heartburn—in babies and children who bore the fatal risks.<sup>29</sup> As will be shown, children whose lives were not at risk of any serious medical condition were put at risk of harm in clinical trials.

The oversight system for the protection of human subjects of research is governed by a series of recommendations in the Belmont Report that were translated into regulations.<sup>30</sup> However, the pharmaceutical industry and its financially dependent research stakeholders tightly control the system.<sup>31</sup> In 2000, Dr. Thomas Bodenheimer provided detailed examples of how industry sponsors were in control of all facets of the process, skewing clinical research and the published reports to present their products favorably.<sup>32</sup> Pharmaceutical sponsors maintain control of research design, including the dose of the drug being tested, the end point of the trial; subject selection criteria; data analysis; and control of publication. Industry sponsors ensure that the entire process is conducted in secrecy, enabling them to suppress negative findings -- even fatal outcomes.<sup>33</sup> Academic based investigators and their institutions have grown beholden to industry, "some have entered into partnerships with drug companies to set up research centers and teaching programs in which students and faculty members essentially carry out industry research."<sup>25</sup> A front page report in *The Wall Street Journal (WSJ)* said that stock analysts don't trust sponsor-paid-for clinical trial reports. To find out the truth, they go directly to those involved in the trials.<sup>34</sup>

Academic and corporate review boards—so-called institutional review boards (IRBs) have regulatory authority to protect the interests of human subjects, but in reality these boards mainly serve the interests of their colleagues, the investigators whose research they evaluate, and the institutions that employ them.<sup>35</sup> Government oversight agencies seem all too willing to promote the interests of the industries they purport to regulate. As Dr. Carl Elliott docu-

mented in his article, "Pharma Buys a Conscience,"<sup>22</sup> bioethicists have also been "bought" by the pharmaceutical industry. The last of the participants in the process are the scientific, peer-reviewed journals, whose flawed peer reviews of submitted clinical trial reports has led to the publication of biased research findings.<sup>37</sup> In short, the current oversight system is compromised by pervasive conflicts of interest. The oversight it provides is often little more than a charade in which ethical corners are cut and industry interests are given precedence over the interests of patients.<sup>38</sup>

### Failure to weed out scientifically flawed research

Few critics of the IRB system have focused on their failure to weed out scientifically unsound research. A fundamental ethical requirement for research involving human beings is that it be scientifically valid. But in the current research climate, IRBs have approved "high risk, high impact" experiments—even when those experiments lacked ethical or scientific justification.<sup>39</sup> In a 1994 editorial in the *British Medical Journal (BMJ)*, Dr. D.G. Altman acknowledged that although scientific criteria are an important part of the evaluation of research proposals, "many ethics committees explicitly take a view of ethics that excludes scientific issues. Consequently, poor or useless studies pass such review even though they can reasonably be considered to be unethical."<sup>40</sup> In an editorial in the *Archives of Pediatric and Adolescent Medicine* in 2000, Dr. William Silverman pointed out that under the current system, poorly designed research proposals that "should have been disqualified before they were ever presented to an IRB for review" have been approved and published without difficulty in peer-reviewed journals.<sup>41</sup> Silverman believes the research review process should be reversed: proposals should first have to pass the rigors of biostatistical analysis before they can be considered by an IRB. The following example involving clinical trials approved by the IRB of the National Institute Of Mental Health (NIMH) validates Altman and Silverman's criticism.

In 1999, following disclosures in *The Boston Globe* about unethical experiments conducted on psychiatric patients, the Director of NIMH, Dr. Steven Hyman, reviewed the ethical and scientific justification of 89 active clinical trials at the institute. He shut down 29 trials and when he discovered that they had failed to meet either ethical or scientific justification or both.<sup>42</sup> The next year, he questioned the merit of speculative, biochemical (so-called) "violence prediction" experiments and other chemical provocation experiments under his authority but many similar such experiments continue to be conducted at other institutions with NIMH funding.<sup>12, 43</sup>

### The human cost

The evidence presented in this paper suggests that children and adolescent lives had been put at risk of harm for profit. Two widely-publicized research-related deaths, of 18-year-old Jesse Gelsinger in a gene transfer experiment at

the University of Pennsylvania,<sup>44</sup> and Ellen Roche, a healthy volunteer who was required to inhale hexamethonium in a nontherapeutic asthma experiment at Johns Hopkins University,<sup>45</sup> illustrate the tragic human consequences resulting from the current climate at academic research centers in which considerations for the safety of research subjects has given way to commercial interests. The 1996 death of 19-year-old Nicole Wan, a University of Rochester student, who volunteered for a MIT-sponsored, nontherapeutic experiment testing airborne chemicals,<sup>46</sup> is less widely known. As will become apparent, regulatory protections can be violated, circumvented, reinterpreted, and/or deconstructed with ease in order to facilitate and speed up the research process. Those at highest risk of exploitation in research have always been the disadvantaged and the vulnerable.<sup>3,4</sup> As will be shown, children who are incapable of protecting themselves have been subjected to painful, nontherapeutic biomedical experiments that were against their own best interests.<sup>47</sup>

*The British Medical Journal* recently published a review of 561 research reports that appeared in five medical journals. The review indicated that in 40% of the reports of studies involving children or adolescents, study investigators had failed even to report whether the procedures followed "were in accordance with the ethical standards of the responsible committee on human experimentation." The review authors concluded that, "Unless we enhance our system of safeguards, an unethical study could be published. While the primary responsibility for assuring ethical conduct of research rests with investigators, peer review journals should be more active in protecting human subjects."<sup>48</sup> In some respects, animal research subjects are better protected in the U.S. than human research subjects, especially children. Under the stipulations of the Animal Welfare Act of 1966,<sup>49</sup> the well being of research animals must be monitored by an independent veterinarian and documented and safeguarded by study researchers.<sup>50</sup> Researchers must justify any pain inflicted on animal subjects, and the Secretary of Agriculture must provide an annual report to Congress accounting for the outcome of every animal in research. There are no comparable requirements concerning children used in clinical trials.<sup>51</sup> As a result, no one is required to collect statistics about how many children overall have been harmed or injured in the course of research. Indeed, a recent report by the Institute of Medicine confirms that no one maintains a record of the number of nature of clinical trials, the number human subjects or their disposition following research.<sup>52</sup> While the number of pediatric clinical trials is increasing dramatically,<sup>53</sup> those who advocate increased recruitment of children for clinical trials fail to acknowledge the underlying risks for children independent of the particular study and the risks that it poses. Furthermore, these risk factors have an impact on children's safety, yet they are not factored in when IRBs evaluate the risk / benefit ratio. Indeed, in case 1 (below), the IRB unanimously approved an invasive, painful experiment on healthy children by disingenuously claiming that

the risks children encountered in a medical research center were "minimal risk" in comparison with "playing in traffic."

Although the FDA has insisted that its oversight process is still the world's gold standard for safety, the agency has come under criticism. Drug safety experts warned that by shortening the drug approval process, the chance for harmful drugs to make it onto the market would be increased. Critics have argued that more should be done to conduct follow-up studies on the safety of new drugs after they have been released for wide use-- so that problems could be caught early. In the process of speeding up the approval of new drugs, FDA would abandon its stated agency mission "to protect the public health by ensuring that drugs are safe and effective."<sup>28</sup> The results of the "fast track" drug approval process, however unintended, were predictable: drug-related injuries mounted, human lives were lost, and the FDA was forced to recall a record number of approved drugs.<sup>54</sup>

In a Pulitzer Prize winning investigative series (1998-2001), David Willman of the *Los Angeles Times (LAT)* found that within one four year period, twelve drugs had been recalled because they killed people.<sup>55</sup> Seven of the drugs had been approved between 1993 and 2000,<sup>56</sup> and three had been recalled within a period of 9 months. Willman noted, "By the end of the 1990s, the FDA was approving more than 80% of the industry's applications for new products, compared with about 60% at the beginning of the decade."<sup>28</sup> Whether the drug approved is beneficial or lethal, Willman noted, the pharmaceutical industry has been making record profits: The seven killer drugs that had to be withdrawn, generated \$5 billion in sales. "The FDA approved each of those drugs while disregarding danger signs or blunt warnings from its own specialists. Then, after receiving reports of significant harm to patients, the agency was slow to seek withdrawals. According to 'adverse-event' reports filed with the FDA, the seven drugs were cited as suspects in 1,002 deaths."<sup>28</sup> For example, approval of the weight-loss drug, fenfluramine,<sup>57</sup> and the diabetes drug, Rezulin, had come under close scrutiny by scientists, including FDA's own experts.<sup>28</sup> Their warning before these drugs' approval --about Rezulin's potential for inducing liver toxicity, and fenfluramine's potential for neurotoxicity--had been largely ignored.<sup>58</sup> Eventually--when the death toll became known to the public--both drugs had to be recalled.<sup>28</sup> Critics of the speed up, including FDA specialists and former officials, charged that senior FDA officials had "lost their compass and . . . forgot who it is that they are ultimately serving."<sup>59</sup> The approval and slow removal of these and other life-threatening drugs lent credence to the criticism offered by such health care analysts as Thomas J. Moore, healthcare analyst at George Washington University School of Medicine and author of *Prescription for Disaster*, told the Star Ledger:

The FDA is more interested in listening to industry rather than their own experts. And the policies are very beneficial to the industry's bottom line. Even

after the problems (with certain recalled drugs) became known...they remained on the market for a time and sold at a huge clip.<sup>58</sup>

According to John Schwartz of *The Washington Post*, Dr. Brian Strom, a professor of medicine at the University of Pennsylvania voiced apprehension about "the disasters that are underway that we don't know about."<sup>60</sup> Even former FDA commissioner, David Kessler, MD, JD, acknowledged in that article, "we didn't go to the wall" against industry to fight for post-marketing surveillance of adverse effects.<sup>60</sup> Raymond Woosley, MD, a leading drug-safety expert and cardiologist at Georgetown University, told Associated Press that he does not take or prescribe new drugs that are on the market less than a year.<sup>61</sup> Perhaps most revealing of all is that FDA commissioner, Dr. Jane Henney, who said she follows Dr. Woosley's advice herself, and advises others to closely question their doctor when he wants to switch to a brand-new remedy.<sup>61</sup> What protections does such a policy offer ordinary citizens whose local physicians are not as well informed as the head of the FDA? Physicians who don't have insider information are not told that the data presented to the FDA prior to its approval of a new drug may be inadequate to ensure its safety.

Since 1997, a continuing stream of scandals were reported mostly in the popular media involving the approval of harmful drugs that had to be recalled, and research practices that had failed to meet ethical standards.<sup>62</sup> These reports revealed the terrible human consequences that followed in the wake of sluggish and ineffective federal oversight and enforcement mechanisms. Research at seven institutions was shut down;<sup>63</sup> federally funded research at another three institutions was suspended entirely;<sup>64</sup> and research was partially suspended at an unspecified number of still other institutions. Government investigations and shut downs between 1998 and 2001 made it clear that only the apparent tip of the proverbial iceberg had been revealed.<sup>65</sup> In September 2000, near the end of her term as Secretary of HHS, Donna Shalala acknowledged in *NEJM*, "I did not expect, or want, to complete my tenure. . . by raising questions about the safety of patients in clinical research. However, recent developments leave me little choice. . ." and: "we have a responsibility to make sure the money we invest -- money that comes from U.S. taxpayers -- is not used in ways that harm people participating in clinical trials or that unnecessarily risk harming them."<sup>13</sup> Unfortunately, the only initiative taken was to reorganize the oversight agency under a new director.<sup>66</sup>

### **A conflict of moral values**

A moral imperative of medical research requires that: "non-therapeutic, non-diagnostic experimentation involving human subjects must be based on true consent if it is to proceed as a human enterprise."<sup>67</sup> That moral principle is rooted in the Nuremberg Code: "The voluntary consent of the human subject is absolutely essential."<sup>1</sup> But children,

who are precluded from exercising voluntary, informed consent, are particularly vulnerable to conflicting interests and coercion. The historical record demonstrates that those who make decisions on their behalf do not always serve the children's best interest. At times, even their parents' interests conflict with theirs. Therefore, children need greater protection from exploitation than do adults. The degree of such protection is in dispute. The issue was hotly debated in the 1970s by prominent ethicists, such as Paul Ramsey and Richard McCormick when the hepatitis producing experiments at Willowbrook came to light<sup>4</sup>. Ramsey argued from the perspective of the child's best interest:

[C]hildren, who cannot give a mature and informed consent... should not be made the subjects of medical experimentation unless, other remedies having failed to relieve their grave illness, it is reasonable to believe that the administration of a drug as yet untested or insufficiently tested on human beings, or the performance of an untried operation, may further *the patient's own recovery*.<sup>67</sup> [Emphasis in original. p. 234]

McCormick argued from the utilitarian perspective, claiming that parents can consent for their children for non-therapeutic experiments because (if they could) children would (or ought to) consent. But even he thought it was permissible only if there are "no discernible risks, no notable pain, no notable inconvenience... almost no cost to the child."<sup>67</sup>[p. 236]

The regulations finally adopted in 1983 restrict the use of children to research that offers a potential benefit to them.<sup>51</sup> To be approvable, research involving "greater than minimal risk [must present] the prospect of direct benefit to the individual [child]." [45 CFR 46.405] If there is even a "minor increase over minimal risk" without a prospect of direct benefit to the individual subjects, the research must "likely ...yield generalizable knowledge about the subject's disorder or condition which is of *vital importance*..." [45 CFR 46.406. Emphasis added] Failing to meet those standards, if an investigator claims a proposed children's research project "presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare children" (in the aggregate), it would have to undergo public scrutiny. Under federal regulations, such a proposal would have to be sent for review under the supervision of the Secretary of Health and Human Services who is required to convene a panel of experts "and provide opportunity for public review and comment." [45 CFR 46.407]

But, as Dr. Leonard Glantz,<sup>67</sup> points out, these regulations have many loopholes, they are ambiguous, leaving wide discretion to institutional review boards (IRBs)-including the determination of how to evaluate "*minimal risk*," "*minor increase over minimal risk*," or "*greater than minor increase over minimal risk*," as well as such regulatory terms as "*potential benefit*," "*the subject's disorder or*

condition." IRBs have defined these terms inconsistently, depending upon local vagaries and the cultural climate at a particular institution.

#### Case 1: Testing insulin sensitivity in obese and normal weight children

In 1996, the IRB at the National Institute of Child and Human Development (NICHD of NIH), approved an obesity experiment to be conducted on 100 obese and 92 normal weight children, aged 6 to 10. The experiment involved fasting, blood tests, X-rays, and a two-day overnight hospital stay during which the children were subjected to the following painful, invasive procedures: insertion of an intravenous line for 18 hours; a battery of intensive measurement of metabolic rates; a two hour hyperglycemic clamp study involving a second IV line for two hours; blood sampling at 5 minute intervals; a three hour hyperinsulinemic clamp study for two hours with two IV lines; infusion of glucose and insulin for 3 hours.

The IRB at the NICHD unanimously approved the experiment on April 24, 1996 under the federal "minimal risk" category. An investigation by the federal Office of Human Research Protections (OHRP) revealed that the IRB had justified its decision as follows: "Several members of the Committee explored the meaning of minimal risk and what a child might encounter in a visit to the doctor or while playing in traffic. It was felt that spending several hours in the Clinical Center in a clamp experiment would be safer than playing actively on sidewalks and streets."<sup>68</sup> Clearly, the meaning and application of the federal standard for "minimal risk" has been stretched beyond its original intent. This experiment was suspended by OHRP.

While not all IRBs would have approved the experiment or classified it as "minimal risk," this inconsistency renders current regulations inadequate to the task of protecting children's rights and welfare. This case and the others to be discussed in this paper demonstrate that the authorizing committees function through a process of disingenuous rationalization. They have approved painful, even harmful experiments that offered no potential direct benefit for the children by trivializing the pain, discomfort and risks to be borne by children. Issues involving informed consent will not be addressed in any depth, as the subject requires another paper.

Glantz notes that some bioethicists have argued that the "mature minor" rule-i.e., permitting children to consent to medical care *intended for their personal benefit*-should be extended to research.<sup>67</sup> Glantz explains that "the policy behind adopting the mature minor rule...has been to facilitate the delivery of beneficial medical treatment to this population." [p.226] However, those who would apply it to research disregard the fact that in the context of research children would be exposed to substantial risks without a direct benefit. Glantz and others who argue from the child's best interest position, note that "better and clearer rules are needed not just to protect children, but also to protect the integrity of the research endeavor itself."<sup>67</sup> [p. 244]

In the opinion of the author, a conflict exists between utilitarian pragmatism (corporate ethics) and principle-based moral values enshrined in the Hippocratic Oath, the Nuremberg Code and the Declaration of Helsinki-which mandate that the rights and best interests of the individual must prevail over the interests of science, commerce or society.<sup>10</sup> Those who argue for broader interpretation of federal regulations to facilitate pediatric trials have made specious claims such as: a child is safer taking a drug under controlled research conditions than under a personal physician's care.<sup>69</sup> But, as Dr. Jane Orient,<sup>70</sup> President of the Association of American Physicians and Surgeons pointed out:

Children who receive a drug tested on adults, as an off-label prescription, arguably are at greater risk than children taking a drug that has already been extensively tested in a pediatric population. However, they are at no greater risk than an experimental subject would be... There is no reason to think that the supervision of a physician who is dedicated solely to patient welfare is less protective than that of a physician who is in the dual role of physician/researcher.

Indeed, as the cases in this paper will reveal, the claims made by research stakeholders are contradicted by the fact that research by its nature involves greater risks than individualized care. And these cases demonstrate clearly that the child's "best interest" standard had not been applied by those who approved them and those who conducted them. Leonard Glantz observed<sup>67</sup> that researchers cannot ignore the legacy of research abuses to which children have been subjected. [p. 215] In the author's view that legacy is not a thing of the past.

#### Case 2: A Bizarre Fatal Pacemaker Experiment

In a 1996 front page article, the *Wall Street Journal (WSJ)* reported the result of its investigation of a government sponsored pacemaker experiment that raised serious ethical concerns about whether the children's lives had been put at risk.<sup>71</sup> Between 1992 and 1996, a National Institute of Health (NIH) team, led by Dr. Lameh Fananapazir, inserted pacemakers into 68 children to test whether the devices could treat or cure hypertrophic cardiomyopathy, an inherited heart disease that can cause thickening of the heart and sudden death.<sup>72</sup> Implantation involved intricately threading 27 inches of wires through the patient's veins. Once situated, the pacemaker was effectively permanent and too dangerous to remove should it fail. *WSJ* reported that, "Physicians complained at meetings and in published letters in medical journals that Dr. Fananapazir's hypothesis about remodeling children's hearts was too radical to test on human subjects."<sup>71</sup> The device's manufacturer sponsored the pacemaker experiment, the trial was supposed to include only children who had not been helped by medication-a less radical alternative.

Nevertheless, Jennifer Munger was recruited into the

experiment. Jennifer had been diagnosed with hypertrophic cardiomyopathy at seven months of age. In 2001, the *Boston Globe* reported that she had been treated successfully with drugs and helped to become an active child, even a cheerleader. Fourteen months after she became a subject in the NIH pacemaker study, she collapsed and died on her school's playground. She was eight years old. *The Globe* reported that for years preceding the study Jennifer's parents had resisted Dr. Fananapazir's efforts to recruit her as a research subject. But after a checkup in which they were told that "the only course for Jen was a pacemaker," they relented.<sup>72</sup> Other families also claimed that "NIH doctors used undue pressure to get their children" into the experiment.<sup>72</sup>

*The Boston Globe* reported that Douglas Gray was a 12-year-old whose condition worsened after the insertion of the pacemaker. His parents later said they had been "stampeded into a pacemaker for their son without even being told it was an experiment."<sup>72</sup> His mother charged that they were told their son would die if they didn't act quickly, but soon after the pacemaker was implanted, Douglas became so weak "he could barely walk the 25 yards to the family's mailbox."<sup>72</sup> After implantation, Douglas was repeatedly hospitalized. Finally, another doctor prescribed a different procedure and one that proved successful-heart-thinning surgery.

This bizarre experiment demonstrates the failure of the system to protect children from experimental abuse even at the nation's premier research institution. Lawsuits were filed by two of the families involved against the doctor and NIH. Even so, NIH refused - and continues to refuse - to provide information about the number of children (out of the 68 involved) who were helped or harmed in the course of the experiment. Government lawyers acted to shield NIH doctor-researchers. Children continued to be recruited for this study in 2002.<sup>73</sup> One mother who had resisted NIH's efforts to recruit her daughter and niece after her sister had died in a similar experiment reasoned that, "Research in children should be treated with 10 times the level of caution as research in adults."<sup>71</sup>

According to Michael Moss whose 1996 report in the *WSJ* brought the case to light, the harshest criticisms of the pacemaker experiment and its recruitment tactics came from former NIH scientists. Dr. Paolo Spirito, for example, was quoted as saying, "It's unbelievable that pacemakers were allowed to be put in children with no severe disease and no symptoms." And Dr. Mark Josephson quipped, "There's a lot of witchcraft here."<sup>71</sup>

### Financial incentives under FDAMA

The Better Pharmaceuticals for Children Act (incorporated into the FDA Modernization Act (FDAMA) was enacted under the intense lobbying efforts of pediatric research stakeholders such as, pharmaceutical industry representatives, government research institutes (NICHD, NIMH) and industry supported organizations such as the American Academy of Pediatrics.<sup>74</sup> There was no consumer input: Abby Mayers,<sup>75</sup> President of the National Organization of

Rare Diseases (NORD) testified in 2001: "Congress, FDA and the regulated industries negotiated the law, and consumers were specifically omitted from the debate." FDAMA offered considerable financial incentives to brand name pharmaceutical companies for engaging children as research subjects. The law extended the length of market exclusivity by six months for any patented drug or one under development that was tested on children in controlled clinical trials. But, as Alexander Tabarrok,<sup>76</sup> of the Cato Institute points out, FDAMA makes "no requirement that the [pediatric] studies demonstrate either safety or efficacy in children, nor need they be sufficient to establish pediatric labeling." Mayers put it this way, "The changes that FDAMA brought about were NOT intended to enhance or protect the public's health... The truth was that life-saving medicines were already being speeded through the process, but the standard "me-too" drugs were taking more time than the industry wanted."<sup>75</sup>

*The Wall Street Journal (WSJ)* reported that six months of market exclusivity for top selling drugs could mean between \$284 million and \$975 million.<sup>77</sup> The financial incentives were awarded on the basis of arguments made by pediatric research stakeholders<sup>78</sup> who claimed that the absence of pediatric dose information for drugs approved for adults puts children at great risk of adverse drug reactions; that only by testing the drugs in children in controlled clinical trials could safe dose information be obtained; and that incentives were necessary to prod drug companies into conducting pediatric trials to provide clinicians who prescribe the drugs for children with needed safety, efficacy and dose information.<sup>79</sup>

However, one needs to examine the veracity of those underlying assumptions. First, physicians in clinical care do have a reliable guide for pediatric dosage schedules such as-the *Harriet Lane Handbook*, published by Johns Hopkins University.<sup>80</sup> Second, arguments have been made by David Healy, MD, for example, that clinical trials are not designed to inform clinicians but, rather, to gain FDA approval either for a new drug or a new use of an old drug, or to change the drug's label.<sup>81</sup> Third, within the strict boundaries of research individual treatment needs must usually give way to the goals of the research. Fourth, decisions about the right dose for a particular patient can only be made by a treating physician whose judgment is based on knowledge of the individual patient's health problems and needs. Clinical observation often provides clinicians far more useful dose information-which usually needs to be individualized-rather than the one-size-fits-all industry recommendations. Indeed, Dr. Jay Cohen,<sup>82</sup> a physician and professor of family and preventive medicine at the University of California, points out, "when new drugs are approved, the experiment is just beginning." [p. 59] He makes the point that adverse medication reactions-which are the fourth leading cause of death in the U.S.-are usually the result of unnecessarily high doses recommended by drug companies. He faults industry for manipulating clinical trial designs, to show high efficacy but hide the negative effects-which enhances marketing. And he also faults



the FDA for allowing industry to get away with it.

It is further claimed, that the benefits to be gained for all children, by conducting clinical trials on some children, outweigh the risks to the test subjects.<sup>19,79</sup> However, those making these claims, and those who set public policy, do not volunteer their own children for experiments involving risks or pain, for the benefit of others. Is it surprising that parents who volunteer their children are often less informed, educated, or financially advantaged than those who do not?<sup>83</sup> The cases described in this paper reveal that FDAMA has had a decisive impact on eroding the interpretation of existing regulations (weak as they are). Since FDAMA, children are at increased risk of being subjected to experiments that put commercial interests ahead of theirs. But society has a moral obligation that overarches scientific or commercial exploration.<sup>1,2,51</sup> A policy that puts the well-being of a child (who is a non-consenting human subject) at risk for the good of others, violates fundamental moral principles and devalues the child as a human being.

#### Case 3: Babies recruited for heartburn drug trial:

Propulsid (cisapride), a drug approved (for relief of heartburn) in 1993, exemplifies how regulatory agency failures can affect children used in research. According to David Willman's Pulitzer Prize winning article for the *Los Angeles Times*,<sup>84</sup> prior to the drug's approval, a medical officer in FDA's cardiology division had noted that EKGs showed that Propulsid prolonged the QT interval, which caused 2.4% of patients in clinical trials potentially fatal irregular heart rate and rhythm disorders. The QT side effect should have raised alarm in the agency: in 1990 two allergy drugs, Seldane and Hismanal, had been withdrawn because the QT side effect had been judged to pose lethal risks. However, following PDUFA, the FDA came under the influence of the pharmaceutical industry and the Propulsid case illustrates the impact of that influence on FDA's approval of the drug, approval of clinical trials that exposed babies to the drug's adverse effects, and finally the lethal consequences following its marketing.<sup>55,56,60</sup> In the same year that Propulsid was approved, FDA's director of cardiology, Dr. Raymond Lipicky, published a warning in the *American Journal of Cardiology*, stating that if a drug prolonged the QT interval and had a benefit that was "less than lifesaving . . . any risk of death would likely be considered unacceptable."<sup>85</sup> FDA's advisory panel failed to consult with the agency's cardiology division before recommending approval of the drug.

Willman reported that by 1995 the FDA's gastrointestinal division had also identified the danger of Propulsid to the heart. The division alerted the manufacturer, Janssen Pharmaceutica, to numerous adverse-reaction reports that indicated that Propulsid was prolonging the QT interval and thereby risking fatalities. Further, Lauren Neergaard, senior science reporter of the *Associated Press*, reported that the FDA informed Janssen in 1996 that Propulsid was "not approvable" for children.<sup>86</sup> Willman reported that by 1997, the director of the FDA's gastrointestinal drugs divi-

sion acknowledged that "at least" three children had died after being given Propulsid. Yet, it was not until June 29, 1998 that the FDA issued a warning to doctors about cardiac problems and infant deaths associated with the drug.<sup>87</sup> Despite knowledge of the drug's deadly side effects, the FDA apparently had allowed clinical trials on babies to continue. One hundred children and babies had been used in drug trials of Propulsid at one hospital alone.<sup>29,88</sup> The babies had been born with gastroesophageal reflux, which is not a life-threatening condition. Gastroesophageal reflux is characterized by "recurrent spitting and vomiting, occurs in about four out of ten healthy children, and doesn't always require treatment."<sup>89</sup> Propping up the baby after feeding and correctly positioning the baby for sleep usually can eliminate the condition;<sup>90</sup> experts agree that most babies outgrow the condition by their first birthday.<sup>91</sup>

In 1999, Propulsid's sales reached \$950 million, while the number of deaths reached 80 adults and children.<sup>92</sup> In that same year, nine month old Gage Stevens was recruited into a controlled, FDA approved, clinical trial and given Propulsid and Tagament for four months. He died of cardiac arrhythmia--as had six-month-old Chase Brown the year before. By the time it was taken off the market, nineteen children who had been given Propulsid had died. The Children's Hospital (Pittsburgh) consent forms that had been signed by the parents of children in the experiment had stated that the FDA had approved Propulsid for use in children.<sup>93</sup> It was a false claim and one that facilitated the way for testing of Propulsid on children. After his death, Gage Stevens' parents said, "Little did we know that Gage was basically a guinea pig, and they never told us that [Propulsid] causes dangerous side effects, or there had been deaths."<sup>94</sup> The final blow was delivered when the baby's parents learned from the autopsy report that his esophagus "failed to show signs of significant inflammation or other hallmarks of gastroesophageal reflux."<sup>95</sup> In other words, the baby didn't have the condition for which he was entered as a subject into a clinical trial.

In hindsight, it can be seen that the FDA bears major responsibility for the deaths of children in the Propulsid trial. Even as the number of deaths mounted, the FDA allowed the drug to remain on the market and incur more human casualties. By April 2000, the death toll had risen to 103.<sup>96</sup> In the end, it was press coverage and public condemnation - not FDA edict - that forced the drug's withdrawal. Janssen Pharmaceutica withdrew the drug "voluntarily" from the U.S. market on July 14, 2000.

#### **Children exposed to drugs with profound pathological side effects**

Psychoactive drugs-including stimulants, antidepressants and antipsychotics-affect the central nervous system in profound ways. Adults and children who are prescribed psychoactive drugs have been led to believe, without any proof, that they have a "chemical imbalance" in their brain.<sup>97,98,99</sup> Demonstrable evidence exists linking these drugs to pathological side effects of varying degrees of severity.

Researchers know that these drugs also produce profound, long-lasting, functional alterations in the brain. Steven Hyman, M.D., a molecular neurobiologist, (until recently) the director of the National Institute of Mental Health, is an expert on the mechanisms by which psychoactive drugs work. In a much-cited 1996 article in the *American Journal Of Psychiatry*, Hyman refers to psychostimulants (amphetamine, methylphenidate, and cocaine) as addictive drugs of abuse. He indicated that whether abused or prescribed, the mechanisms by which psychoactive drugs work-including psychostimulants, antidepressants and anti-psychotics-- are the same.<sup>100</sup>

Furthermore, Hyman wrote, "chronic administration of psychoactive drugs creates perturbations in neurotransmitter function" which "cause molecular and cellular changes in neural function." [p. 151] Hyman explained that repeated "perturbations" (i.e., chronic use of psychoactive drugs) "usurp normal homeostatic mechanisms within neurons" (i.e., interfere with normal brain function) "thereby producing adaptations that lead to substantial and long-lasting alterations in neural function." [p. 153] Hyman noted that these neural adaptations might not be beneficial to the organism. Indeed, in the case of stimulant drugs, Hyman stated, the adaptations result in addiction.

#### Case 4: Ritalin (methylphenidate) a Prescription for Dependency?

The FDA classifies Ritalin (methylphenidate) and the other drugs that are prescribed for attention deficit hyperactivity disorder (ADHD)-including Ritalin, and the amphetamines, Adderall and Dexedrine-as Schedule II controlled substances. This class of drugs includes, cocaine, methamphetamine, morphine, opium and barbiturates-these are drugs with the highest abuse potential and dependence profile in medical use.<sup>101</sup> In 2000 testimony, the federal Drug Enforcement Administration (DEA) indicated that in 1994, the DEA was petitioned by an advocacy group, children and adults with ADHD (CHADD) requesting that methylphenidate be removed from the list of schedule II controlled substances.<sup>102</sup> CHADD claimed that methylphenidate was a mild stimulant with little abuse potential. DEA conducted an extensive review of the use, abuse liability, actual abuse, diversion, and trafficking of methylphenidate. The agency's conclusions were documented in its 1995 report: Methylphenidate, it found, shares the same profile of dependency as the other schedule II stimulants, notably, addiction. The DEA also noted that "despite the unprecedented availability of other highly abusable stimulants like cocaine and methamphetamine, methylphenidate is still highly sought after by the drug abusing population."<sup>103</sup> The petitioners subsequently withdrew their petition. Although FDA approved Ritalin for use in children with ADHD over the age of six, it is prescribed even for toddlers.<sup>104</sup>

In 1995, Dr. Nora Volkow of Brookhaven Laboratories reached the conclusion that the mechanism of action of cocaine and Ritalin (methylphenidate) is almost identical.<sup>105</sup> Ritalin (methylphenidate) "works" in children

much as cocaine "works" in adults -- it sharpens short-term attention span in whoever takes the drug, whether or not they have been diagnosed with ADHD. And, Dr. Volkow found, Ritalin stays in the brain much longer than cocaine. The most common side effects of Ritalin are insomnia, appetite suppression, and weight loss.<sup>106</sup> A congressional panel raised concerns as early as 1970, about whether Ritalin and other the drugs used to treat children with ADHD were creating dependency whether the children who were being prescribed psychostimulant drugs "are involved in a psychological game of chance that may or may not affect their future."<sup>107</sup> In 2000, Dr. Hyman acknowledged that given the lack of clinical data about the safety and efficacy of psychoactive drugs in children, "every child who receives this medication represents an uncontrolled experiment - that is entirely unacceptable."<sup>108</sup>

One of the few studies to examine long-term effects on children prescribed drugs that stimulate the central nervous system (CNS) is a 26-year Berkeley study conducted by Dr. Nadine Lambert who evaluated 492 children, in the San Francisco Bay area, half of whom had been prescribed Ritalin (methylphenidate) for ADHD.<sup>109</sup> Dr. Lambert found strong evidence significantly different lifetime tobacco dependence rates--40% for those who had been exposed to Ritalin as children compared to 19% for age-mate controls. And the rates for cocaine dependence were 21% for the Ritalin -ADHD group, and 10% for age-mate controls. Dr. Lambert reported her findings in 1998 to a NIH panel of experts, suggesting that one explanation for the higher dependency rates to tobacco and cocaine among former Ritalin and amphetamine users is a "sensitization hypothesis" based on her interpretation animal studies showing that early exposure to stimulant drugs predisposes rats to the reinforcing impact of cocaine.

Other adverse drug effects include cognitive impairment, aberrant behavior, involuntary facial tics and Tourette syndrome.<sup>110</sup> In 1996 FDA issued a warning about a possible risk of cancer based on two studies on mice and rats.<sup>111</sup> Of particular concern is the discovery that millions of children are being prescribed various psychoactive drugs for disorders that lack objective diagnostic criteria.<sup>104</sup> They are often used in an effort to control or modify undesirable behavior. Children whose brain is still in development, are prescribed these drugs in an uncontrolled experiment-even as concerns are being raised about the risks of addiction, cancer, and the possibility of causing neurological damage.

#### **The science behind the ADHD diagnosis**

In 2001, Dr. Benedetto Vitiello, Director of Child and Adolescent Treatment and Preventive Interventions Research Branch at NIMH, acknowledged a fundamental medical ethics requirement: "the ability to formulate a valid and reproducible diagnosis of disorders and syndromes is a prerequisite for clinical trials."<sup>112</sup> [p. 985] That essential prerequisite is lacking in pediatric psychopharmacology trials. Millions of children in the U.S.

have been diagnosed with loosely defined psychiatric "disorders," for which they are prescribed a variety of psychoactive drugs that pose significant hazards even though the diagnoses for which the drugs are prescribed have not been scientifically validated. Indeed, experts do not agree about the criteria for diagnosing children's behavioral disorders-as objective diagnostic tools do not exist. Indeed, experts do not agree about the best method for treating children's behavior disorders. In 1998, NIH convened a panel of experts to evaluate the evidence about ADHD. The experts failed to reach a consensus about either the diagnosis or treatment of ADHD.<sup>113</sup>

Some of the compelling arguments before the NIH consensus panel were made by physicians who are critical about the overuse of psychiatric drugs in children. Several of these experts questioned the validity of pathologizing "behavior disorders" altogether. For example, neurologist Fred Baughman, M.D., psychiatrist Peter Breggin, M.D., and neurologist-pharmacologist Sydney Walker, M.D., questioned the validity of the ADHD diagnosis and charged those who promote drugs for children are in collusion with the drug industry.<sup>114</sup> Others charged that those who promote prescribing psychotropic drugs for ADHD are not influenced by science but by culture, politics, and money. Moderates, such as pediatrician William Carey, M.D., (Children's Hospital, University of Pennsylvania) lamented the fact that the current diagnostic system in psychiatry ignores both differences in individual temperament and the probable contributory role of the environment. Instead, health practitioners think "the problem is supposedly all in the child."<sup>115</sup> Lawrence Diller, M.D., a pediatrician, expressed concern about the use of Ritalin as "a performance pill" a short term "fix" rather than a long-term solution for a troubled child.<sup>116</sup>

In its final statement the 1998 NIH panel of experts acknowledged:

The risks of treatment, particularly the use of stimulant medication, are of considerable interest. Substantial evidence exists of wide variations in the use of psychostimulants across communities and physicians, suggesting no consensus among practitioners regarding which ADHD patients should be treated with psychostimulants... However, there is no evidence regarding the appropriate ADHD diagnostic threshold above which the benefits of psychostimulant therapy outweigh the risks....Finally, after years of clinical research and experience with ADHD, our knowledge about the cause or causes of ADHD remains largely speculative. Consequently, we have no documented strategies for the prevention of ADHD.<sup>113</sup>

In 1999, the Agency for Healthcare Research and Quality (AHRQ, formerly Agency for Health Care Policy & Research) conducted a review of 78 peer reviewed, published, ADHD studies that were randomized and controlled (RCT), in an effort to answer the following two ques-

tions:<sup>117</sup>

1. What is the evidence from comparative studies on the effectiveness and safety, both short and long term, of pharmacological and nonpharmacological interventions for ADHD in children and adults?
2. Are combined interventions more effective than individual interventions?

The findings of the AHRQ review are summarized succinctly on pages 4-5 of their report: "overall, numerous deficiencies in the reporting of available randomized controlled trials (RCT) limit the assessment of their validity, relevance, precision, and, therefore, their clinical application. Most studies did not clearly describe clinically important information such as the primary outcomes of interest... compliance with treatment, and baseline measurement of outcomes." The authors stated that they could not conduct a comparative analysis of the findings because of "the low quality of reporting and the large number and heterogeneity of outcome measures and tests used in the studies." [p. 4-5]

The AHRQ reviewers indicated that the studies failed to report the most critical data necessary to answer the two questions. In 87% of the studies, the number of dropouts and withdrawals and the reasons for such withdrawals were not described, and neither were the long-term effects and severity of the adverse effects. The authors noted, "no comparative studies were identified with data on important adverse effects of interest, including potential for abuse of stimulants, liver toxicity due to pemoline, or major arrhythmia with tricyclic antidepressants in patients with ADHD." Thus the AHRQ report concluded: "These limitations increased the likelihood of biased results."

The AHRQ report stated that the findings of these scientifically flawed studies "show a trend to general improvement over time regardless of treatment... Ritalin appears to reduce behavior problems in ADHD children as long as it is taken," but there is little evidence of improvement in academic performance. The authors noted that few studies followed children for a period of time equivalent to the length of time children typically remain on these treatments, and no information was provided about the reasons so many children discontinued the drug.

Just as an NIH panel of experts failed to reach a consensus about ADHD, these independent research evaluators found no evidence in the ADHD research literature to substantiate the claims made by proponents of psychoactive drug treatment for ADHD. Reports in the professional literature,<sup>103,104</sup> and in the press,<sup>118</sup> showed evidence that American children are being prescribed psychoactive drugs, singly and in "cocktails" with dubious medical justification. And, as will be demonstrated, children are also being recruited to test psychoactive drugs in clinical trials, often against their best interest.

In February 2000, *JAMA* published a report by Dr. Julie Zito et al validating earlier reports about widespread pre-

scription of potent psychoactive drugs to very young children, questioned the medical justification for such practice.<sup>119</sup> An accompanying editorial by Dr. Joseph Coyle of Harvard University, pointedly observed, "Given that there is no empirical evidence to support drug treatment in very young children and that there are valid concerns that such treatment could have deleterious effects on the developing brain, the reasons for these troubling changes in practice need to be identified."<sup>120</sup>

At the height of controversy about the appropriateness of prescribing psychoactive drugs for behavioral problems, in 2000, the American Academy of Pediatrics (AAP) published an ADHD clinical practice guideline.<sup>121</sup> The guideline appears to be an effort by this professional organization to legitimize the ADHD diagnosis even though it fails to meet medical diagnostic standards. The AAP guideline acknowledged the absence of any objective criteria to support the ADHD diagnosis, [p. 1162] but AAP maintained that a "consensus" exists about the DSM-IV criteria. The DSM-IV-diagnostic statistical manual-is psychiatry's catalog of observed disorders and conditions it deems pathological. However, on the same page, AAP acknowledged that the DSM-IV criteria "remain a consensus without clear empirical data supporting the number of items required for the diagnosis;" the criteria "remain subjective and may be interpreted differently by different observers." [p. 1163] AAP also acknowledged that current ADHD criteria do not take into account gender differences or developmental variations in behavior," [p. 1163] and that "symptoms may not be apparent in a structured clinical setting" [p. 1160] suggesting that symptoms are bound up with "the demands and distraction of the home and school." [p. 1160] The AAP guideline also acknowledged that "the questions on which [ADHD] rating scales are based are subjective and subject to bias." [p. 1164] Finally, the AAP guideline acknowledged that "brain imaging studies and electroencephalography do not show reliable differences between children with ADHD and controls." [p. 1167] Nevertheless, the organization endorsed an ADHD diagnosis in children 6 to 12 on the basis of the (admittedly unscientific) DSM-IV criteria and reports (from parents and teachers) of "inattention", "hyperactivity", "academic underachievement", or "behavior problems. None of these reported "symptoms" prove the existence of an underlying pathology.

Even without a firm basis for diagnosing children with psychiatric disorders, highly influential child psychopharmacologists at major academic research centers-including NIMH and the American Academy of Child and Adolescent Psychiatry (AACAP)-advocate psychoactive drugs for the treatment of children whose behavior is bothersome. These psychiatrists tend to brush aside concerns about the long-term risks of these drugs. For example, Drs. Benedetto Vitiello, Peter Jensen, and Laurence Greenhill, whose work is supported by pharmaceutical companies and the NIMH, claim that the rate of ADHD in the U.S. is 3% to 5%. They also claim that even if drugs are overprescribed, ADHD is under diagnosed.<sup>122</sup>

Greenhill claims, "The percentage of U.S. youth being treated with psychostimulants is well within the estimates of the prevalence of ADHD."<sup>123</sup> Jensen asserts that "only about one-half the children with ADHD are getting treated."<sup>108,124</sup> They deny that there is any problem with overprescribing stimulant or psychoactive drugs for children. But a University of Massachusetts study found that less than one percent of elementary school children in the United Kingdom are diagnosed with ADHD. The study author concluded from that comparative statistic that ADHD may be culturally specific rather than biologically produced.<sup>125</sup>

Dr. Larry Stone, former president of the AACAP, describes physicians who prescribe psychoactive drugs to children as "pioneers searching for a new path through the wilderness." He claims that "child psychiatrists (who) treat children with medications are doing an outstanding job, and they are doing it in spite of a lot of concern about both the media opinion-makers and the potential for lawsuits."<sup>126</sup> And Harvard's pediatric psychopharmacologist, Dr. Joseph Biederman claims "ADHD is one of the best researched disorders in medicine; in fact, the overall data on its validity are far more compelling than for many other medical conditions."<sup>127</sup>

In March 2000, Matthew Smith, a 14 year old boy, died suddenly while on a skateboard. The chief medical examiner of Oakland County (Michigan), Dr. Ljubisa Dragovic, concluded that the boy's death from cardiac arrest was caused by long-term exposure to Ritalin. He told *WebMD News*, "this was a gradual development... the boy's small blood vessels showed scarring and tissue growth consistent with chronic stimulant use."<sup>128</sup> The medical examiner's report stirred immediate controversy: psychiatrists insisted the drug was not to blame but Dr. Dragovic insisted, "the finding was comparable to what you'd see in an adult who has abused amphetamines or cocaine for years." He told the *San Jose Mercury News*:

if you continuously and repetitively bring in this kind of drug... for months and years -- the body will show changes, and these are the changes we saw in the heart of this kid. There was no other underlying condition, no other illness or disease, no other drug. Only a background of 10 years of continued use of methylphenidate (Ritalin ).<sup>129</sup>

Whether or not it is possible to ascertain that Matthew died solely from the adverse effects of Ritalin, there is concern about whether the long-term exposure to the effects of stimulants may cause ill effects in some children. As will be shown, numerous reports in the scientific literature have linked "sudden death" in children to psychoactive drugs.

#### Case 5: Multimodal Treatment ADHD (MTA) Study:

Influential proponents of psychostimulant drug treatment for ADHD-including the Research Unit on Pediatric Psychopharmacology (RUPP), the American Psychiatric Association (APA), and the AACAP<sup>130</sup>---have hailed the

MTA study "a landmark in the history of treatment research in child psychopathology."<sup>131</sup> Others are unconvinced about the justification of using psychostimulants for children whose behavior may be within the range of normalcy,<sup>132</sup> and criticized the study for lack of scientific rigor and bias.<sup>133</sup> The NIMH-sponsored, Multimodal Treatment ADHD Cooperative Group study (MTA), was conducted between September 1992 and August 1997. Two official reports by the investigators were published in the *Archives of General Psychiatry*, Dec. 1999.<sup>134</sup> The articles profiled a multi-site study in which 579 children, aged 7 to 10 and diagnosed with ADHD, were selected out of 4,541 screened for participation in the experiment. MTA was conducted over 14 months at 10 research centers, and included four treatment regimes ("arms") to which children-subjects were randomly assigned. Children received either (1) medication management alone, (2) combined medication management and behavioral therapy, (3) behavioral treatment alone, or (4) community care which included psychoactive drugs. The purpose of the study was to find the most effective long-term treatment for ADHD. However, there was no follow-up planned beyond 14 months.

The "findings" of the MTA study are a matter of dispute: there were no trained professionals to observe and evaluate either the children's symptoms or adverse drug reactions. Parents reported side effects of varied severity in 63.7%.<sup>135</sup> [p.1073] It is unclear how a placebo washout was conducted or how many children dropped out because of adverse reactions. The children's behavior was rated improved on the study medication intervention groups (1) and (2) by their parents and teachers, but not by blinded classroom observers who found no difference among the 4 intervention groups.<sup>136</sup> As was noted in previous studies,<sup>117</sup> researchers acknowledged that the children's academic performance did not improve.<sup>137</sup> It is unclear how many of the 579 children who began the study completed it.

The investigators' analyses have focused attention mostly on whether drugs alone or a combination of drugs and behavioral therapy improved children's behavior.<sup>138</sup> Oddly, one of the key findings of the study-and a finding not accentuated by the original study researchers or ever cited by later researchers who have cited the original study-was that "more than three fourths subjects receiving behavioral treatment were successfully maintained without medication throughout the study." [p. 1083] Several factors complicate the debate surrounding experiments like MTA. In seeking to test use of psychoactive drugs in children, investigators pretend that objective criteria exist for diagnosing children with pathological behavioral problems-when they do not. And they fail to address the fundamental ethical question: "whether conditions in children and adolescents are sufficiently serious and disabling to necessitate pharmacologic intervention?"<sup>120</sup> Lacking a firm basis for diagnosing and isolating only children with pathology, it is difficult, if at all possible, to justify exposing healthy children to the known adverse effects of the

drugs. Furthermore, there are indications that some of the psychoactive drugs being given to children are known to researchers and the FDA to be ineffective for the purpose intended. Antidepressants are an example of drugs prescribed for children (in clinical care and research) that have raised doubts about both efficacy and safety.

In FDA's "Background Comments on Pediatric Depression," (2000) Dr. Robert Temple, director, Office of Drug Evaluation at the FDA, acknowledged "the preponderance of negative studies of antidepressants in pediatric populations."<sup>139</sup> All but a single pediatric study that tested antidepressants in children resulted in negative findings. That single study compared Prozac to placebo in 96 children-48 in each of two test arms. The recovery differential at the end of the study between Prozac and placebo was only 8%.<sup>140</sup> Yet, children continue to be prescribed antidepressants-both the older tricyclics (TCAs) and the newer SSRIs. Numerous reports have linked these drugs to serious adverse effects and potential long-term harm. TCAs have been linked to cardiac arrhythmias,<sup>141</sup> and "sudden death."<sup>142</sup>

Since 1995, Dr. Madelyn Gould, epidemiologist at New York State Psychiatric Institute, has been studying the relationship between "sudden death" in children and the use of psychoactive drugs. In her grant application to the National Institute of Mental Health, she stated, "If the patient is a child or adolescent and the medication is being prescribed for a non-life-threatening psychiatric condition . . . even the suspicion of an association between a psychoactive medication and death among children may have major ramifications for the use of the drug . . . Restriction of the use of the medication may be warranted."<sup>143</sup> Curiously, her findings have not been published.<sup>144</sup> Rather than restricting the use of psychoactive drugs in children, the trend unfortunately continues to increase the exposure of ever-younger children to psychoactive drugs.<sup>119,145</sup>

Influential psychopharmacologists who prescribe psychoactive drugs for children in clinical practice and research-often prescribing these drugs singly and in combination-do not appear to be guided by the child's "best interest" principle. For example, Dr. Biederman has recommended the use of TCAs in the treatment of children with ADHD, claiming "there is a substantial body of literature documenting the efficacy of tricyclic antidepressants on ADHD in over 1,000 subjects."<sup>146</sup> But as indicated above, even FDA's director of drug evaluation expressed concern that "at least 12" of pediatric antidepressant drug studies found the drugs ineffective.<sup>147</sup> Furthermore, the risk of serious harm for children should give pause about prescribing these drugs for conditions that are not life-threatening. Extraneous factors may get in the way of impartial diagnosis, selection of study subjects, the test comparator, and an impartial evaluation of the results. As Leonard Glantz told the *New York Post*, "Obviously, if it's the researchers doing the diagnosis, it is in their interest to diagnose kids with ADHD because they need them for the study."<sup>148</sup>

### **The impact of FDAMA on children:**

The financial incentives provided to the pharmaceutical industry giants under FDAMA have been discussed above. Those incentives also had a major impact on the other biomedical research players-academic and government research institutions, professional associations, and scientific journals-all of who benefited from the opportunity FDAMA provided for expansion of pediatric drug trials. Thus, all research stakeholders profited financially as a result of FDAMA. For example, in 1999, the National Institute of Child Health and Human Development (NICHD) expanded the network of pediatric pharmacology research units created in 1994 at key academic institutions from 7 to 13 units. Dr. Robert Steinbrook reported in the *NEJM* that the network "has conducted many of the studies related to pediatric exclusivity and the pediatric rule, and that additional funding for the units is planned."<sup>149</sup> In 1994, the FDA issued a new regulation-the "pediatric rule"-requiring drug manufacturers to find data to support label changes for pediatric use. If the information was insufficient, the rule required the label of the drug to state that "safety and effectiveness in pediatric patients have not been established."<sup>150</sup> In 1997, the "pediatric rule" was codified in FDAMA, a law that was passed without first addressing either ethical problems or the negative impact it might have on children.<sup>75,77,151</sup> FDA did not issue a risk assessment statement to inform congress and the public about the potential unintended consequences for children that would likely result from the legislation. In fact, the law did not lead drug companies to study drugs in children for life-threatening conditions.<sup>149</sup> Effectively, pharmaceutical industry interests to expand, and when advantageous, to create new markets, were allowed to take precedence over children's best interest.

In the opinion of the author, financial incentives have been a catalyst for the recruitment of children to test patent-protected, best selling drugs-without regard for the children's best interest. Congress failed to request an impact assessment of the new law or to balance the financial incentives provided to industry with improved safeguards to protect children from harm. Congress did not provide safeguards against child exploitation, nor did it ensure that market exclusivity incentives would lead to studies of vital medical importance for children. The (brand name) pharmaceutical industry and its lobbying arm, the Pharmaceutical Research and Manufacturers of America (PhRMA), are accused of distorting the public health goal intended by those who enacted FDAMA. These companies are demanding exclusivity "for virtually any study in pediatric subjects, no matter how trivial the study design, and regardless of the [absence of] medical significance or utility of the data obtained."<sup>152</sup>

Children, who had no voice in the adoption of the legislation, and are legally precluded from exercising the right to refuse, were targeted to bear the burden of testing drugs so that drug companies could qualify for a highly lucrative six-month patent extension. FDAMA also loosened restrictions on off-label uses of drugs,<sup>153</sup> thereby further

enhancing market rewards for industry. Unfortunately, the law failed to balance financial incentives with new (or improved) safeguards to protect an increased number of younger and younger test subjects in clinical trials. The predictable consequences of wider recruitment of children as test subjects, without added protection to compensate for their greater vulnerability, became clear after children had been put in harms' way. Indeed, a recent study has shown that children are at greater risk from medication errors when hospitalized than adults.<sup>154</sup>

In 2001, Alice Dembner of the Boston Globe examined research conducted with children since 1994. She found that children had suffered and died in clinical trials in which ethical standards had been violated.<sup>155</sup> Children were-and continue to be-recruited with Toys 'R Us gift certificates and induced to assume risks in drug trials not in their own best interests. Parents in need of money were offered as much as \$1,000 to "volunteer" their children for drug experiments that involve risks of harm.<sup>53</sup> Physicians engaged in coercion and violated the Code of Ethics of the American Medical Association<sup>156</sup> by accepting \$5,000 referral fees (kickbacks) for recruiting the children.<sup>157</sup>

These financial incentives for parents and physicians to offer children for experimentation demonstrate a debasement of the children's humanity. In the last seven years alone, according to Dembner, at least eight children died in medical experiments and hundreds suffered harmful side effects. Given the tendency of researchers not to report adverse events in clinical trials and given the fact that the number of child research subjects has grown from about 16,000 in 1997 to about 45,000 in 2002, "there is strong reason to believe that deaths and injuries in research involving children are more widespread" than available statistics would indicate.<sup>155,158</sup>

### **Shift in Federal policy: FDA / NIH revise guidelines**

The FDA acknowledged that before FDAMA, the use of children as subjects in phase I safety drug studies, "had been primarily limited to life threatening diseases and children who had the disease" in question.<sup>159</sup> Prior to FDAMA, public policy, though not always the practice, was shaped by the 1983 federal regulations that restricted the recruitment of children for their protection from experiments that are not in their best interest. Following FDAMA, however, federal policy shifted, some might say, retreated from a policy that protected children to one that led to their exploitation. Dr. Steinbrook reported in the *NEJM* that between 1991 and 2001, FDA approved 341 new drugs and biologics, 69 of these (20%) were labeled for children at the time of approval. Between 1991 and 1997 FDA collected data on those new drugs and biologics to determine whether any were potentially useful in children<sup>149</sup> In 1997 FDA suspended its tracking of new drugs to acquire that information. One might speculate that the reason for this suspension is that research stakeholders were no longer restrained by the moral imperative to protect children from research not specifically intended for their benefit. Indeed, Dr. Rosemary Roberts, FDA's

Deputy Director of Pediatric Drug Development, lent support to an expansionist pediatric policy in her public presentation by adopting the rallying cry of the American Academy of Pediatrics: "There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents."<sup>19</sup>

In March 1998, NIH issued policy guidelines for grant applications stating that children "must be included in all human subjects research, conducted or supported by the NIH unless there are scientific and ethical reasons not to include them."<sup>160</sup> The ethical considerations prompting the adoption in 1983 of additional federal regulations for the protection of children, was to minimize the exposure of children to the risks of experimental research. It is difficult to find any ethical considerations prompting NIH officials in 1998 to remove the restrictions that had been imposed to protect children. Clearly, other, more powerful interests competed with children's welfare and the safeguards enacted to protect their best interests were overturned. In 2002, Congress extended the financial incentive provision of FDAMA for five years, and enacted additional measures "to stimulate pediatric studies for drugs under development and drugs no longer patented."<sup>161</sup> But an analysis by Alexander Tabarrok concluded:

Pediatric exclusivity is a poorly targeted program. Rather than creating incentives to discover information about the drugs most valuable to children, it encourages pediatric studies on the drugs most valuable to adults.<sup>76</sup>

**Deconstructing Federal regulations: the "at risk" hypothesis**  
 FDA's Pediatric Advisory Subcommittee (PAS) issued a consensus statement noting that: "In general, pediatric studies should be conducted in subjects who may benefit from participation in the trial. Usually this implies the subject has or is susceptible to the disease under study." However, the PAS indicated that it had utilized "a broad definition of potential benefit" and gave the example, "*otitis media*" (middle ear infection) claiming, "any child has the potential to benefit from a treatment for *otitis*."<sup>162</sup> By claiming that all children are potentially "at risk" of a future condition, they argued that every child might potentially derive a benefit from testing a new treatment for a condition they are deemed to be "at risk." Essentially the recommendation justified the inclusion of all children in experiments involving risks of harm with no potential direct benefit.<sup>159</sup> Leading child psychiatrists at NIMH, Drs. Vitiello,<sup>163</sup> Jensen, and Hoagwood, declared: "a particular category of potential research subjects is that of children who do not present with disorders or psychopathology but are considered at risk for mental illness." (p. 1046) The NIMH investigators offer no scientific basis for that "at risk" assumption. Dr. Vitiello and colleagues have also argued for a relativist approach to the assessment of risk: "the interpretation [of minimal risk] varies across clinical context, institutional settings, and

IRBs." (p. 1046) They further proposed that in nontherapeutic research-where there is no potential benefit for the child subject-the determination of risk level should be the ratio between risk and "the scientific value of the project." (p. 1048) This is curious in light of their own acknowledgement: "Thus far, research on the biological substrates of mental illness has yielded relatively little specific information on the pathogenesis of psychiatric disorders." (p.1045) By their own acknowledgement, the experiments they defend have yielded no scientifically valuable information. Children were victimized in experiments that yielded no information of scientific value. They had to endure painful procedures-such as lumbar punctures, drug washout, and chemical provocation ("challenge")-in experiments that were designed to induce psychosis, panic attacks, and depression. The experiments yielded no information of clinical or scientific value.

An example cited by Vitiello and NIMH colleagues is a 1998 experiment conducted at the New York State Psychiatric Institute (NYSPI)<sup>164</sup> in which 6 to 12 year old children were exposed to carbon dioxide. They defended the experiment and its classification as "minimal risk" stating: "To study ventilatory physiology in children with anxiety disorders, both patients and normal subjects have been exposed to 3% to 5% carbon dioxide for 15 minutes. The procedure does not entail risk for physical harm, but it can briefly trigger anxiety." [p. 1046] Most of the pediatric psychiatry experiments cited by Vitiello et al, fail to meet either ethical standards or scientific justification. Theirs is a chilling deconstruction of medical ethics based on the "best interest of the child."

At FDA's pediatric subcommittee deliberations (November 5, 1999) it was suggested that the regulatory definition of "minimal risk" (i.e., "probability and magnitude of harm encountered in everyday life")<sup>51</sup> does not exclude *death*: "a risk of everyday life includes death." It appears that at least some members of the research community, among them some members on FDA's Pediatric Advisory Subcommittee, suggest that for research purposes, death may be classified as a "minimal risk." By arguing for a broad standard to be applied to the definition of "potential benefit" and "minimal risk" children were effectively deprived of existing, more protective federal regulations. The new policy essentially, if not explicitly, sanctions the exploitation of children who lack the legal ability to give or withhold informed consent, and are therefore, incapable of protecting their best interests. The FDA advisory panel consensus statement ends with a disingenuous recommendation that FDA "adopt the principles described in Subpart D."

A further indication of a shift in policy to accommodate industry's need to expand the pool of research subjects was an article by the director of the federal Office of Human Research Protection, Dr. Greg Koski, in which he made the following statement in 2000: "as we understandably increase the extent to which needed research is conducted on vulnerable populations, such as children, it may well be necessary to *redefine* our notions of *consent* and *assent* for

purposes of recruiting subjects" (emphasis added)<sup>165</sup> It is especially disturbing that the head of the agency charged with enforcing federal regulations indicated the intent to "redefine" legal concepts --such as informed consent--which is defined in law and is mandatory for any research involving human beings. The doctrine of informed consent is not merely a "notion." This intent to "redefine" fundamental legal rights in order to facilitate research is a radical departure from federal law, which recognizes informed consent only by a competent adult. The law recognizes the vulnerability of children (under 18). Children who are deemed legally incapable of exercising informed consent are precluded from volunteering to research. But research stakeholders are attempting to appropriate the "mature minor" standard, to broaden its application. They would equate research that exposes a child to risks with medical treatment whose purpose is to reduce risk of harm by providing a therapeutic intervention to benefit the child.<sup>67</sup>

This stunning reversal of federal policy was accomplished through a backdoor strategy of reinterpreting regulatory language rather than by going through the more transparent regulatory process. Federally appointed advisory committees opened the door for the use of healthy children to serve as experimental subjects without requiring a bone fide medical justification.<sup>166</sup> The advisory committee was used to lend legitimacy to the recruitment of children to test drugs whose safety was uncertain, to subject them to discomfort and risks of harm (some foreseeable, others not) on the basis of a presumed potential risk for which there is no empirical evidence. The case of nine-month old Gage Stevens who died in the Propulsid experiment is a tragic example of such a policy.<sup>167</sup>

A recent article in the *NEJM* reported that after 1997 the FDA stopped tracking data that revealed whether drugs under development may potentially be useful in children.<sup>149</sup> In 1999, the FDA acknowledged that the post-FDAMA policy changes "led to an increasing number of proposals for studies of safety and pharmacokinetics, including those in children who do not have the condition for which the drug is intended."<sup>151</sup> One can only speculate about the scope of the negative impact these policy changes have had on children who had been subjected to risks in drug trials that were not necessarily in their best interest. One can infer that healthy children suffered from a reversal of FDA's policy announce by FDA's Associate Director of Pediatrics, Dr. Dianne Murphy, who was reported to have stated at a conference (April 3, 2001): "FDA will no longer accept information submitted to the agency for pediatric exclusivity if the data is derived from children who are not patients and for whom there is no foreseeable benefit."<sup>168</sup> That said, the same report indicated that FDA was "upset that pharmaceutical companies are continuing to enroll healthy children in clinical trials." Then why doesn't the FDA turn down data obtained in those studies?<sup>169</sup> What, one wonders, is holding the FDA back?

For Eli Lilly, a six-month extension of market exclusivity for Prozac (fluoxetine) can mean \$831 million.<sup>77</sup>

This windfall is especially welcome, since Prozac sales have slumped. FDAMA also hastens the pace of bringing new drugs into the pediatric market before the safety of the drugs in adults is known--that is, before the adverse side effects have become known. This new policy puts children at increased risks of being prescribed harmful drugs both in clinical practice and clinical trials. The policy contradicts the advice of FDA's own commissioner, who cautioned against taking a new drug until its adverse effects are known, for at least one year after it has been on the market.<sup>61</sup> Since Dr. Jane Henney's comments addressed safety precautions for adults, it is difficult to understand the rationale of using children like canaries in the mines to test the safety of those drugs.

### **A market-driven children's mental health crisis**

An increased number of children are being exposed to psychotropic drugs for various behavior problems that do not rise to the level of pathology.<sup>119,53,81,114,115,116,122</sup> Increasingly, these drugs are prescribed in controlled and uncontrolled trials.<sup>170</sup> This paper suggests that the catalyst for both the sharp rise of psychiatric drug testing in pediatric research and physicians' widespread over-prescribing of these drugs to children is FDAMA. Dr. Coyle, in his editorial in *JAMA*, expressed alarm at evidence of wide misuse and overuse of psychoactive drugs in children, emphasizing: "that there is no empirical evidence to support psychotropic drug treatment in very young children and that there are valid concerns that such treatment could have deleterious effects on the developing brain." Dr. Coyle called the practice "a crisis in mental health services for children."<sup>120</sup> The practice also drew embarrassing criticism in the popular press. Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania observed in *Business Week*, "There's either a strange plague of hyperactivity in the U.S., or we've got a lot of folks prescribing Ritalin as a psychopharmacological nanny." In the wake of the Zito and Coyle articles in *JAMA*,<sup>119,120</sup> there were calls for a federal investigation.<sup>172</sup> NIMH director, Dr. Steven Hyman, asked, "How can we tolerate a situation in which drugs are prescribed to an increasing number of preschoolers without safety and efficacy data?"<sup>173</sup> Yet, NIMH has initiated few, if any, retrospective outcome surveys to determine whether psychoactive drugs have done more harm than good to the generation of children to whom they have been widely prescribed. First Lady Hillary Clinton convened a White House Conference to address public concerns in the wake of the Zito and Coyle articles--essentially it was one of a series of efforts at "political damage control."<sup>174</sup> Several class action lawsuits were filed involving Ritalin and antidepressants.<sup>175</sup> In the end, however, the 2000 White House conference participants--who interestingly did not include Dr. Zito--did not call for the kind of retrospective follow-up studies that might have provided much-needed details for rational decision-making without putting additional children at risk of harm. Neither did the conference participants call for curbs on the prescription of psychoac-



tive drugs for children.

Mental health professionals and government officials did not criticize the inappropriate prescribing that Dr. Coyle decried, instead they issued reports claiming that the U.S. "is facing a public crisis in mental healthcare for infants, children and adolescents,"<sup>174</sup> and that "approximately one in five (21%) children and adolescents (aged 9 to 17) experience the signs and symptoms of a DSM-IV disorder during the course of a year."<sup>176</sup> The same reports claimed that 11% of children have significant functional impairment. No doubt, such claims have led to increased diagnosing and prescribing of psychoactive drugs in some cases children have been coerced by doctors, teachers, or school administrators to take the drugs-sometimes even when their parents have opposed use of those drugs.<sup>177</sup>

What followed instead of curbing drug use in children was an aggressive campaign led by organized psychiatry called for new initiatives to expand testing of these drugs in young children in clinical trials.<sup>178</sup> Those who "informed" the deliberations and the reports of other high level conferences-were psychopharmacologists from NIMH, RUPP, the APA, and the AACAP, essentially invented a children's "mental health crisis."<sup>174</sup> The "remedial" action taken was to initiate pediatric trials testing psychoactive drugs in children as young as three. Ostensibly the trials are to test if psychotropic drugs are safe for children, but in fact they are conducted to obtain data for submission to the FDA whose approval of the drugs for children would lend legitimacy to the practice and protect prescribing doctors from liability. The stepped up testing of psychotropic drugs in children was facilitated by the enactment of FDAMA, which has proven to be a financial boon to stakeholders in psychopharmacology.

It is significant that Dr. Vitiello<sup>112</sup> acknowledged an "unprecedented" increase in pediatric psychopharmacology while conceding (repeatedly) "the diagnostic uncertainty surrounding most manifestations of psychopathology in early childhood." [p. 983] He wrote: "pediatric psychopharmacology has recently seen an unprecedented expansion... NIMH-funded research for clinical trials in youths has more than doubled in the last few years." [p. 987] Furthermore, Dr. Vitiello acknowledged the impact of FDAMA noting that in addition to the financial incentives for industry (that were discussed above), FDA's "Pediatric Rule" authorized the FDA to require drug companies to conduct studies on children to test drugs currently in development for use in adults "whenever a potential use in children can be anticipated."<sup>179</sup> But since FDA stopped tracking drugs under development to ascertain whether "a potential use in children can be anticipated,"<sup>149</sup> it was left to the drug companies to make such claims.

In October 2000, NIMH and FDA representatives met to discuss the *need* to *develop* psychopharmaceuticals for young children.<sup>180</sup> The pediatric advisory panel provided FDA with a broad interpretation of current federal regulations, in effect, lifting the regulatory restrictions on the use of healthy children as research subjects. FDA's policy shift after FDAMA, has encouraged the medical research com-

munity to apply broader standards when evaluating an anticipated need or research "benefit" for healthy children who, it is argued, might possibly become ill at some future time. Thus, healthy children who do not meet the criteria of a diagnosable disorder or condition are being sought as "risk bearing" subjects to test drugs whose safety is unknown (even in adults), for disorders they may never have. In the wake of FDAMA, children are being stripped of the protections they had gained in 1983 and are at risk of exploitation. Indeed, FDA's Associate Director of Pediatrics, Dr. Dianne Murphy, alluded to that possibility when she included the following statement in her presentations: "Children must not become a commodity."<sup>181</sup> But without a firm basis for diagnosing only children with pathology, it is difficult to justify exposing children to the known adverse drug effects, and the possibility of long-term changes in neural function. The following cases demonstrate how young children even toddlers have been exploited in experiments as means to an end.<sup>182</sup>

#### Case 6 Preschool ADHD Treatment Study (PATS)

The preschool ADHD Treatment Study (PATS) was launched by NIMH in November 2000, to test Ritalin in young three to five year old children. The institute's director of Child and Adolescent Treatment and Preventive Interventions Research Branch, Dr. Vitiello, acknowledged the "uncertainty about the diagnosis of mental disorder in preschoolers." Indeed, he noted, this uncertainty "precluded FDA from requesting studies of psychoactives in younger children."<sup>112</sup> [p.987] He further acknowledged, "Only limited data exist on the efficacy and safety of antidepressants and mood stabilizers in school-age prepubertal children. Clinical trials of these agents in preschoolers do not seem possible given the current uncertainties about diagnostic validity of mood disorders in children <6 years old." [p.985] Despite the acknowledged "uncertainty about the diagnosis" NIMH initiated this \$5 million, multi-site, government sponsored experiment that will expose 312 three-year-old children to psychostimulant drugs without any validated medical condition or evidence demonstrating that the benefits of using pharmacologic intervention outweigh the risks for the children. The experiment is designed to test the safety and short-term effects of those drugs and the children's tolerance to Ritalin (methylphenidate) at increased doses -- from 2.5 mg once a day, to 15mg three times a day. The parents are to be paid \$645 if their child completes the 43 study visits, and teachers will be paid \$340 to fill out rating forms.<sup>183</sup>

The study's principal investigator, Dr. Lawrence Greenhill, acknowledged in *Science* that ADHD is "not a well-defined psychiatric disorder in this age group."<sup>108</sup> Without a well-defined diagnostic basis, doctors who prescribe controlled substances are on professionally shaky ground. Given that the safety of these drugs has not been established and there is reason to believe that permanent harm may be caused to the central nervous system and brain of the children exposed to the drugs,<sup>100,105,103,109</sup> the experiment would seem to be highly questionable, if not

altogether unethical. The investigators cannot provide any scientific evidence to validate an abnormal medical condition in the children being recruited. Neither can the investigators guarantee that these children will not be harmed. Psychopharmacologists have argued that it is safer to expose children to these drugs under controlled clinical conditions than to rely on pediatricians and primary care physicians to prescribe these drugs (essentially) in uncontrolled clinical trials.<sup>112</sup> No one has provided any scientific evidence validating an abnormal medical condition in the children they have recruited for psychiatric drug trials.<sup>120</sup> Indeed, Dr. Vitiello acknowledged that "very little research has been done to demonstrate replicability across raters and external validity of these diagnoses in preschoolers."<sup>112</sup> [p. 986] The safety and efficacy of these drugs for children has not been proven,<sup>139,140</sup> nor have studies been conducted to determine the long-term outcomes for children who had already been prescribed psychostimulant drugs in past trials, whether conducted with or without controls. Therefore, there is no justification for exposing children to risks as test subjects in psychoactive drug trials.

Curiously, those advocating psychoactive drug tests on three-year old children fail to mention in their grant proposals or publications the findings of one of the few long-term Ritalin follow-up studies. Dr. Nadine Lambert's 26-year follow-up study in the San Francisco bay area that showed evidence of cocaine and tobacco addiction in 40% of adults who had taken stimulant drugs compared to 19% in those who had not.<sup>109</sup> They also ignore the "startling finding" by an expert team of Brookhaven laboratory researchers headed by Dr. Nora Volkow, who in August 2001 reported that by using advanced imaging techniques (positron emission tomography, PET) to examine the effects of addictive drugs-cocaine and methylphenidate (Ritalin)--on the brain, they found that "instead of being a less potent transport inhibitor than cocaine, methylphenidate was more potent."<sup>184</sup> A report in JAMA about Volkow's finding, states that a typical dose of Ritalin given to children (0.5 mg/kg) blocked 70% of dopamine transporters compared to 50% blocked by cocaine. Dr Volkow told JAMA: "the data clearly show that the notion that Ritalin is a weak stimulant is completely incorrect."<sup>184</sup>

Additionally, the question arises, whether investigators who are already convinced that children should be treated with psychoactive drugs at an early age, can be impartial judges about whether the treatment under study poses greater risks than potential benefits. Dr. James Swanson Director of Pediatrics (University of California at Irvine), one of the PATS study investigators, expressed his unreserved certainty, when he said: "treatment can mean the difference between a kid ending up at Berkeley or ending up in prison."<sup>185</sup> Investigators with an a priori conviction may find it difficult to perceive any evidence that undermines that assumption. Finally, many of the investigators involved in the RUPP, MTA, and PATS studies may have conflicts of interest.<sup>186</sup> Those conflicts are not disclosed in the informed consent documents or in published clinical

trial reports. NIMH director, Dr. Hyman, tried to justify the PATS experiment when he stated: "Without good clinical data, every child who receives this medication represents an uncontrolled experiment - that is entirely unacceptable."<sup>108</sup> However, Dr. Hyman's solution is equally unacceptable morally.

Is it morally acceptable to ask little children to assume risks by testing the safety of psychoactive drugs they may not need? The PATS experiment was designed to increase the dose beyond "effective" levels, to test the limit of the child's tolerance at which point the child will likely suffer discomfort. Such an experimental design is clearly not in any child's best interest. Is it morally acceptable to subject children to the discomfort and risk of dose tolerance tests in order to accumulate "good clinical data?" If that rationale were endorsed, it would follow that children could be put at risk to test the safety of various products whose safety is uncertain to provide "scientific" information for the good of many other children. For example, children are at risk of brain damage from exposure to lead paint poison. Does it then follow that as a society we would allow some children to be exposed to lead paint in controlled clinical trials to find out how to protect other children? As will be shown in case 9, researchers conducted such an experiment.

#### **Marketing happiness--Prozac:**

The launching in 1988 of Eli Lilly's fluoxetine (Prozac), the first of the new antidepressants (called selective serotonin reuptake inhibitors, SSRI) was a watershed in psychotropic drug marketing. It set the stage for news reports, such as a 1990 cover story in Newsweek, which extolled Prozac as "the breakthrough antidepressant is easier to prescribe and has fewer side effects. And that makes patients -- and doctors -- happy."<sup>187</sup> Prozac and other SSRIs that followed were promoted as "magic bullets" safer, more effective, with few, and significantly milder side effects than earlier drugs. Prozac sales climbed from \$135 million in 1988 to more than \$2.8 billion in 2001.<sup>188</sup> Institutional psychiatry has been richly rewarded for collaborating with pharmaceutical companies, uncritically extolling the wonders of SSRIs (and atypical antipsychotics) in the scientific literature, at conferences and in the media.<sup>189</sup> SSRIs have been touted as a breakthrough, safe treatment for depression and the prevention of suicide, as well as a wide range of "conditions" such as grief, shyness, and social dissatisfactions--in a word, all-purpose psychoanalgesics.<sup>190</sup> Although scientific evidence of the drug's efficacy was lacking,<sup>191</sup> promotional endorsement by doctors, celebrities, and advocacy groups coupled with their wide application for newly invented "conditions" added to the perception that SSRIs are safe, "magic bullets." It is puzzling that evidence has not shown a decreased rate of suicide since the advent of antidepressant drugs, so it is unclear on what basis it has been claimed that antidepressants reduce the risk of suicide.

#### **Randomized controlled trial bias in psychopharmacology:**

Dr. David Healy,<sup>192,196</sup> a leading U.K. psychiatrist and historian with an international reputation, questions the validity of claims made on the basis of biased randomized controlled trials (RCT). Dr. Healy (and others) have questioned their scientific value, objectivity, and generalizability inasmuch as RCTs do not address scientifically valuable questions. The selection criteria for RCTs suffer from bias ("samples of convenience"), effectively excluding most patients for whom these drugs are ultimately prescribed. Dr. Healy has argued that RCTs are designed to provide companies with results that will provide data acceptable for FDA licensure and marketing purposes; namely, findings that lend support to the claim the drug's effect is "superior to placebo." But finding an effect does not prove treatment effectiveness, or greater benefit to patients than no treatment. He points out that when a treatment effect is therapeutically significant (rather than merely statistically significant), RCTs are unnecessary. They are needed when the effect of treatment is miniscule, in which case large scale RCTs provide answers. But small, statistically low power placebo controlled trials-such as those in which SSRIs were tested-do not inform clinicians about whether the new drug is as good as older drugs, nor if it is effective for patients with severe depression, inasmuch as only patients with light or moderate depression were selected to test the drugs. Their small size and short duration ensure that only the most obvious and frequent adverse reactions will be revealed during RCTs-not the most severe but less frequent side effects. Therefore, the results are skewed and not generalizable for individual patients.

An article in the *American Journal of Psychiatry* by Dr. Mark Zimmerman<sup>193</sup> and colleagues, found that 86% of patients treated for depression at their Rhode Island outpatient clinic failed to meet clinical trial selection criteria. Dr. Zimmerman is quoted saying: "We are not aware of any other medical condition in which individuals with the disorder are routinely excluded because they are not sick enough."<sup>194</sup> He further suggested that selection criteria that limit entry to a "pure" patient pool ensure "positive" results from an unrepresentative group. Understandably drug companies favor the RCT system as it allows them to find only the positive effects they seek. Yet, these manipulated "findings" are then generalized and applied to a much larger patient pool. "Drug companies have been correct in assuming that if they show their medicine works for a highly select group of depressed patients, physicians will use it for all patients."<sup>194</sup>

Thomas Moore sees weaknesses in the entire drug testing system, as it fails to ensure that drugs intended for long-term treatment ever receive long-term testing. In an Op Ed in the *Boston Globe*,<sup>195</sup> he notes that "the legal structure of our drug-approval laws has been built around simpler drugs such as painkillers and antibiotics-which are taken for short periods of time with effects that are more immediately apparent." The author believes failure of clinical trials to provide safety information about the effects of long-term use is at the heart of the debate about the legiti-

macy of prescribing psychotropic drugs for children. Concerns have also been raised about risks posed by "Disorders Made to Order"<sup>190</sup>-i.e., disease marketing campaigns such as, "National Depression Awareness Week." Although they boost sales for drug companies, Dr. Healy<sup>196</sup> points out that such campaigns may result in increased, inappropriate prescribing of antidepressants for mildly depressed patients for whom the drugs' risks are unjustified: "The act of diagnosis by 'medicalizing' experience without being able to remedy it, may itself be an iatrogenic injury." [p.103]

#### **Efficacy Claims Contradicted by FDA Data:**

Several recent analyses of RCT reports submitted by drug manufacturers to the FDA for licensure purposes became publicly accessible, ironically, through a provision of FDAMA. These documents reveal that contrary to widely publicized assertions, evidence shows SSRIs were no more effective than placebo, after all.<sup>191,197,226</sup> The companies' own data corroborate the findings of a comprehensive, independent analysis of SSRI efficacy and outcome measures conducted in 2000 in the UK by Dr. John Geddes<sup>198</sup> and colleagues. They examined 98 RCTs that included a total of 9, 554 patients, of who 5,044 were given SSRIs and 4,510 received alternative antidepressants. The Geddes team concluded that there was "no clinically significant difference in effect" between SSRIs and TCAs. In his article, *Hard to Swallow*, Moore<sup>191</sup> sheds light on FDA psychotropic drug advisory committee deliberations that invariably end with the approval of drugs that have no demonstrable therapeutic value. He reports that overwhelming poor RCT results did not preclude FDA approval, concluding:

"The real message the FDA and the experts were sending was that the efficacy standards for approving drugs for depression were remarkably low. A drug that had a marginal effect at best, and by strict rules no beneficial effect at all was deemed acceptable for aggressive marketing to doctors and patients. Serzone's repeated failures to achieve the expected benefits would not be included in the information disclosed to doctors." [online p. 3]

The documents submitted to the FDA also reveal the scope and severity of adverse side effects experienced by the subjects in those trials-including a significant risk of suicide in psychiatric drug trials.

#### **Safety Issues: the dark side antidepressants (SSRIs):**

While evidence of the therapeutic effect of Prozac (fluoxetine) in depressed patients is in doubt (equally for the other SSRIs), the drug has a dark side.<sup>196</sup> By 1997, Moore pointed out Prozac generated more adverse drug reaction reports than any other drug in America.<sup>191</sup> Between 1987 and 1995, at least 35,230 cases of adverse drug reaction (ADR) reports were filed with the FDA.<sup>199</sup> Among the severe ADRs that were reported (at least 500 times per

reaction) were the following: convulsions, agitation, abnormal thinking, hypertension, cerebro-vascular accidents, sleep disturbances, nightmares, mania, psychosis, severe anxiety, tremors, liver dysfunction, depression, sexual dysfunction. Other serious concerns involve severe withdrawal syndrome<sup>200</sup> and drug-induced suicide. The FDA reportedly received 2,000 reports of deaths from suicide between 1988 and 1997.<sup>201</sup> FDA's own calculations indicate that these reports reflect only 1% to (at most) 10% of adverse events experienced by patients.<sup>202</sup> If those 2,000 reports represent 10% of actual suicides, that would mean that between 20,000. If, on the other hand the reports represent 1% of actual suicides, then 200,000 patients prescribed Prozac may have committed suicide.

Case reports in the lay and scientific literature reveal an array of adverse reactions such as: involuntary muscle spasms, facial tics, extrapyramidal side effects,<sup>203</sup> and extreme agitated restlessness (akathisia). These have raised concerns about whether the antidepressant drugs produce permanent neurological damage with long-term use. In his book, *Prozac Backlash*, Dr. Joseph Glenmullen<sup>204</sup> of Harvard compares the neurological damage of SSRIs to the damage caused by antipsychotics. He speculates that future generations may look back on use of antidepressants and other damaging psychiatric drugs as "a frightening human experiment."<sup>205</sup> Dr. Joseph Coyle raised concerns about the drugs' potential to harm for children's developing brain.<sup>206</sup> Recent findings by Dr. Madhu Kalia<sup>207</sup> and colleagues detected brain damage in rats within four days of high dose exposure to one of four SSRIs - Prozac, Zoloft, Dexfenfluramine, or Sibutramine. Following cessation of drug administration, they found the animals' brains showed marked changes in nerve terminals that release the neurotransmitter serotonin: "We don't know if the cells are dying... There is the potential that this could be happening. This study in animals is a red flag that perhaps we shouldn't use these drugs with reckless abandon."<sup>100,120,207</sup> But muted red flags in the scientific literature don't reach either the public or prescribing clinicians. The media, which is saturated with drug and disease marketing campaigns by industry influences the public, as do promotional copy masquerading as scientific "findings." Clinicians are influenced by reported clinical trial reports that are controlled by the companies with a stake in the results.<sup>32</sup>

#### Case 7: Case reports link suicide to SSRIs :

In 1990, at the height of the Prozac promotional blitz, senior Harvard researchers, Dr. Martin Teicher and Dr. Jonathan Cole, and a psychiatric nurse, Carol Glod, released a fly into the ointment when they reported that six patients who "developed intense, violent suicidal preoccupation" after two to seven weeks of taking Prozac.<sup>208</sup> The authors estimated the risk of developing violent suicidal preoccupation on Prozac (fluoxetine) to be 3.5%. Numerous other case reports of suicidal acts followed. In 1991, senior investigators at Harvard and the University of North Wales (UK) reported similar findings, the apparent

emergence of suicidal ideas.<sup>209</sup> In July 1992, two senior researchers from UCLA, Dr. William Wirshing and Dr. Theodore Van Putten,<sup>210</sup> reported that their patients with no prior history of suicidal behavior "became suicidal during treatment with fluoxetine...all described their distress as an intense and novel somatic-emotional state; all reported an urge to pace that paralleled the intensity of the distress; all experienced suicidal thoughts at the peak of their restless agitation; and all experienced a remission of their agitation, restlessness, pacing urge, and suicidality after the fluoxetine was discontinued." [p. 580] They went on to note: "our cases appear to confirm that certain subjects experience akathisia while taking fluoxetine ... Further, like the akathisia in the neuroleptic-treated schizophrenic population, 'fluoxetine akathisia' can apparently be associated with suicidal ideation, sometimes of ruminative intensity." [p. 581]

In 1993 Dr. Teicher and colleagues added additional fuel to the controversy when they reported:

"Although antidepressants diminish suicidal ideation in many recipients, about as many patients experience worsening suicidal ideation on active medication as they do on placebo. Furthermore, at least as many patients attempted suicide on fluoxetine and tricyclic antidepressants as on placebo."<sup>211</sup>

Psychiatry under the influence of industry did not initiate any controlled studies to confirm or disprove the increased risk for a small number of patients. Instead, Lilly officials (and later officials of other SSRI manufacturers) defended their product by arguing that in the absence of controlled clinical trials to confirm a suicide risk, none exists. In a sworn affidavit, Dr. Cole<sup>212</sup> indicated that such claims by drug companies are "ridiculous" since RCTs are not the place to look for infrequent, but potentially lethal side effects, case reports reveal them. For the most part, the profession has been reluctant to examine or report treatment related adverse drug reactions-"bad drug reactions rarely get well studied."<sup>212</sup>[p.5] Those in the profession who did voice concerns about the drugs' hazards in public were marginalized, maligned, or ignored.<sup>213</sup> Several claimed to refute the Teicher findings<sup>214</sup> others, Dr. Cole points out, have even retracted their published negative findings.<sup>209</sup> or (as will be made clear below) made efforts to draw favorable conclusions from unfavorable results.

Dr. Jick<sup>215</sup> and colleagues conducted the first epidemiological study comparing the suicide rate in 172, 598 patients who had been prescribed one of 10 antidepressants during a five- year period. They found that the risk for patients taking Prozac (the only SSRI prescribed) was 189 per 100,000 patient years, which they stated, "seems to be substantially higher than that of the other antidepressants." [p.215] The authors attempted to deflect that finding by suggesting that "confounding factors" inflated the Prozac risk. However, Dr. Healy, who reviewed the evidence in 1994,<sup>216</sup> analyzed the Jick study (within the context of submitting expert testimony in a U.S. court).<sup>217</sup> His

analysis led him to conclude that the Jick study finding is consistent with others—patients taking Prozac were at greater than (at least) twice the risk of suicide than those taking the reference drug.

### **The Lilly lawsuits:**

Not until 200 lawsuits involving Prozac had been filed,<sup>218</sup> did previously confidential internal company documents come to light in two lawsuits.<sup>217,219</sup> The documents shed light on just what and when Eli Lilly knew about Prozac-induced violent, suicidal and homicidal ideas and acts in some patients during clinical trials.<sup>217</sup> Lilly's own documents revealed that the company knew as early as 1978 - 10 years before its approval in the U.S.—that in some patients, Prozac induced agitation, psychosis, akathisia and restlessness—which are believed to be precursors of suicide:

There have been a fairly large number of reports of adverse reactions... Another depressed patient developed psychosis... Akathisia and restlessness were reported in some patients... Some patients have converted from severe depression to agitation within a few days; in one case the agitation was marked and the patient had to be taken off [the] drug...<sup>219</sup>

According to the *Guardian*<sup>219</sup> report Lilly took the precaution of adding benzodiazepines "to control the agitation" in future pre-marketing trials. The addition of benzodiazepines, no doubt, produced results favorable for FDA approval, but was this addition ever disclosed in published reports to alert other clinical investigators? In May 1984, the British Committee on Safety of Medicine (FDA equivalent) raised concern in a memo to Lilly: "During the treatment with the preparation [Prozac] 16 suicide attempts were made, two of these with success. As patients with a risk of suicide were excluded from the studies, it is probable that this high proportion can be attributed to an action of the preparation [Prozac]."<sup>219</sup> The German drug licensing authority delayed approval of the drug, citing Lilly's own studies showing that "previously nonsuicidal patients who took the drug had five times the rate of suicide or suicide attempts as patients on older antidepressants."<sup>220</sup> When it was approved in Germany the Prozac label included a warning that use of the drug carried a risk of suicide, recommending that sedatives be given along with it. The American public and prescribing doctors have not been similarly warned.

Psychologist, Richard DeGrendpre<sup>221</sup> reports that internal Lilly documents reveal that in 1985 company officials knew the magnitude of the risk and insufficient benefit:

The incidence rate [of suicide] under fluoxetine therefore purely mathematically is 5.6 times higher than under the other active medication imipramine. ... The benefits vs. risks considerations for fluoxe-

tine currently does not fall clearly in favor of the benefits. Therefore, it is of the greatest importance that it be determined whether there is a particular subgroup of patients who respond better to fluoxetine than to imipramine [a non-SSRI antidepressant], so that the higher incidence of suicide attempts may be tolerable. [p. 9]

While it is true that some profoundly depressed patients are at risk of suicide, the profoundly depressed are mostly excluded from clinical trials,<sup>193</sup> and SSRIs are prescribed for even minor dissatisfactions.<sup>190,191,196,204</sup> And they are widely and inappropriately prescribed for children.<sup>112,119,126</sup> By Lilly's own calculations, in clinical trials, Prozac increases the incidence rate of suicide by more than 5 times that of imipramine. If Prozac (and the other SSRIs) increases the risk of violence leading to self-injury, suicide, or even murder in some patients, however small the percentage of patients affected—whether 1 in 100 or 1 in 200—those risks magnify greatly when millions of people—including children—are prescribed these drugs. Dr. Cole<sup>212</sup> cites two studies by Dr. Seymour Fisher<sup>222</sup> and a University of Texas team who reported that 1 in 200 patients prescribed Prozac reported new suicidal ideas while none did in the comparison group prescribed trazodone (an older non-SSRI antidepressant). [p.6] Based on suicide reports received by the FDA,<sup>199</sup> the possibility exists that at least 20, 000 patients who were prescribed Prozac committed suicide. Dr. Healy<sup>223</sup> makes the point that the suicide rate for people with severe depression is 600 per 100,000, but Prozac and the other SSRIs are marketed and prescribed for millions of people who may be mildly or moderately depressed, for whom the risk of suicide "is probably less than 35 per 100,000." [p. 374] The Jick<sup>215</sup> finding of 189 per 100,000 corresponds with Lilly's own finding of a five fold increased risk of suicide.

Investigative reporters and authors who covered the legal battles and examined internal Eli Lilly documents note that Lilly went to extraordinary lengths to suppress that information about Prozac's life-threatening risk, to prevent it from reaching the public and clinicians who prescribe the drug.<sup>224</sup> Dr. Cole notes that "in this day of high grant monies and some dependence on drug company support [ ] so many distinguished experts avoid testifying for plaintiffs...and even disavow their own studies."<sup>212</sup> [p.7] Writing in the *California Lawyer*, Michael J. Grinfeld observed: "The history of Prozac litigation reads like a mystery thriller, filled with allegations of backroom deals, hidden agendas, and unethical behavior."<sup>225</sup> The aggressive marketing and legal defense strategy demonstrates that while pharmaceutical companies reap extraordinary financial benefits from unprecedented, extended patent protection because they are perceived as providing life-saving products, the companies knowingly sacrifice patient safety to increase sales. Even more disturbing is collusion by the FDA. The agency, as will be shown, has had ample evidence about the emergence of uncharacteristic violent suicidal and homicidal thinking when treatment

was begun but did nothing to protect unsuspecting patients or, for that matter, unsuspecting clinicians.

**FDA data confirms that suicide is a significant risk in psychiatric trials:**

The incidence of suicide-preoccupation, attempts, and completion-in patients testing the new psychotropic drugs in clinical trials occurred with disturbing frequency, far exceeding the risk for patients on placebo.<sup>191,227</sup> In 2000, Dr. Arif Khan<sup>226</sup> and colleagues reviewed FDA reports "in order to assess the safety and efficacy of placebo in antidepressant clinical trials." FDA pre-approval data revealed that patients on placebo were actually far less likely to commit suicide than those testing an investigational drug--especially antidepressants and so-called atypical antipsychotics. Among the 19,639 patients testing seven SSRIs in clinical trials, 34 patients had committed suicide and 130 attempted suicide. Of these, two patients who committed suicide and 15 of the suicide attempters were in the placebo arm. In 2002, Dr. Kahn presented an expanded analysis of the data at a NIH sponsored conference, reporting that between 1985 and 2000, more than 71,604 patients participated in clinical trials testing all psychotropic drugs.<sup>227</sup> They found that despite efforts to exclude suicidal patients from clinical trials, the suicide rates were exceedingly high in clinical trials of short duration. The suicide rate for test subjects within a year of testing an atypical antipsychotic was 752 per 100,000 persons (5%) and for those testing an SSRI the suicide rate was 718 per 100,000 (3.7%). Independent analyses of FDA data essentially corroborate the Teicher,<sup>208</sup> Cole and Glod findings and those reported by Jick<sup>215</sup> and others.<sup>209,210,222</sup> FDA data clearly show an increased suicide risk (one in 120 adult patients) for previously non-suicidal patients taking SSRIs. The catalyst that is thought to trigger suicidal or homicidal ideation in some patients is akathisia,<sup>228</sup> drug induced severe restlessness, anxiety and agitation. In September 2000, the British Medicines Control Agency required a warning about the possible risk of suicide on the label of Prozac (and other SSRIs).<sup>229</sup> FDA has not only failed to require disclosure of those life-threatening risks but has been instrumental in keeping the public and clinicians who prescribe the drugs in the dark. Eli Lilly (and the other SSRI manufacturers) has strenuously denied any relationship between Prozac and the emergence of suicidal thoughts or actions, successfully fending off a multitude of lawsuits over the years.<sup>230</sup>

The professional literature, which informs clinicians who treat millions of patients, is heavily weighted with selective, industry- financed (and controlled) reports that inflate positive results, while obscuring the negative.<sup>32,81,98,193</sup> For example, Lilly scientists conducted, what they called a "meta-analysis" comparing the suicide rate of patients in its pre-marketing database with those on placebo. Beasley et al claimed:<sup>231</sup> "Multiple data sources were searched to identify patients with suicidal acts, finding no increased risk." [p. 685] The influential study has been criticized for its selective inclusion criteria: of 27,000

patients in clinical trials, it selected only 3, 065 for analysis, excluding the most relevant patients -those who had suicided and those who had dropped out after developing akathisia.<sup>216,219</sup> The Beasley study also failed to report that many patients in the trials were taking benzodiazepines during Prozac trials. Neither RCT reports nor the drug label informs clinicians or the public about risks that could be fatal. Case reports, ad Dr. Cole, notes, may in fact be a more reliable source of clinically useful information.<sup>212</sup> No doubt, public ignorance about the underlying hazards these drugs pose, and aggressive marketing campaigns to consumers and doctors, influenced both to assume the drugs were safe. Clinicians are not warned about the risks or informed about the need for close monitoring when initiating SSRIs, therefore patients are at increased risk should they develop suicidal symptoms. This may, in part explain why doctors have prescribed the drugs for children widely and inappropriately.<sup>119,126,170</sup> As a result, children have suffered severe adverse effects<sup>232</sup> some have been driven to injure themselves, even to suicidal acts.<sup>233</sup>

**SSRIs prescribed for children with "reckless abandon:"**

Although SSRI's had until recently been approved for use only by adults over the age of 18, they have and are being widely and often inappropriately prescribed for children, without medical justification or evidence of safety.<sup>119</sup> What's more, they are being prescribed to younger and younger children, singly and in combination with stimulants and antipsychotics.<sup>234,119</sup> In 2000, Dr. Jerry Rushton found that Prozac, Zoloft and Paxil were being prescribed widely for children not only for depression, but also for school phobia, anxiety disorders, bed-wetting, eating disorders, and ADHD. "One of the biggest questions this study raises is whether the children who are prescribed both types of medication have both types of disorders, or whether their physicians are recommending these medications for other reasons."<sup>235</sup> Consider the case of Simon, a 29 month toddler who was subjected to an uncontrolled drug experiment. Dr. Lawrence Diller<sup>236</sup> described the following medical travesty in the *Washington Post*: "I was flabbergasted when I later learned from his mother that Simon saw a highly respected child psychiatrist and was now taking Lithium, Zoloft, and Risperdal, three psychiatric drugs at once." Dr. Diller concluded, "I didn't know who felt crazier, Simon or I."

FDA statistics compiled by an industry research firm indicate that Prozac "was prescribed 349,000 times to pediatric patients under 16-including 3,000 times to infants under 1 year of age."<sup>126</sup> It is hard to fathom why doctors would prescribe an antidepressant to infants, since the risks outweigh any conceivable benefit-not to mention the far-fetched belief that infants could be depressed! But it is also true, as has been shown, that clinicians have been kept ignorant about the underlying potential for severe adverse side effects. And most clinicians who prescribe psychoactive drugs for children are unaware of scientists' suspicion that the drugs may cause irreversible neurological damage, nor are they aware about the risk of suicide.

Children, even more than adults, have endured severe adverse effects in clinical trials. As noted above, FDA officials have commented about the poor findings in almost all pediatric trials testing antidepressants.<sup>139</sup> Reports about pediatric trials in the scientific literature are uninformative about the true results. Indeed, a recent Canadian survey by Dr. Klassen et al found that more than 40 per cent of medical studies conducted on children are never published, the results get buried. They traced unpublished data that had been presented at the Society for Pediatric Research and found that *invariably the findings were negative*, raising questions about the safety and/or effectiveness of new treatments. Since many of the drugs were subsequently brought to market anyway, parents and clinicians are often misled about treatments that are not nearly as safe or effective as they had been led to believe in essentially fabricated reports. Some have suggested that this skewing of the scientific literature is a form of "scientific misconduct."<sup>238</sup> There is every reason to believe that an examination of U.S. pediatric clinical trial data would confirm Klassen's findings.

**Children at risk of suicide in psychotropic drug trials:**

In 1991, Dr. Robert King and colleagues at Yale published one of the few reports about the emergence of self-destructive, suicidal behavior in children and adolescents during treatment with Prozac.<sup>239</sup> They noted the need to study the incidence of medication-related agitation, self-injury and emerging suicidal obsession in children taking SSRIs. But neither NIMH nor the FDA has initiated such study. The case of a 13-year-old Kansas City boy, Matt Miller, is a tragic example. The parents told the press that after a few days on Zoloft, the boy "began showing signs of intense nervousness and agitation. He couldn't sit still. He kept kicking people under the table. His eyes were sunken and he couldn't sleep yet he had a restless energy. After six days on the drug, on July 28, 1997, Matt hanged himself in his bedroom closet."<sup>240</sup>

Case 8: Children testing sertraline (Zoloft):

In the mid 1990s Pfizer conducted several pediatric trials testing sertraline (Zoloft) in children and adolescents with obsessive-compulsive disorder (OCD), for the purpose of gaining FDA approval for OCD. One trial was reported in *JAMA*<sup>241</sup>, two in the *Journal of the American Academy of Child & Adolescent Psychiatry*.<sup>242,243</sup> FDA data shows that not only were children in those trials subjected to increased suffering in clinical trials designed to test the maximum dose they are able to tolerate, but they were put at risk of violent eruptions, self-injury and suicide. In a March 1996 letter to Pfizer, Dr. James Knudsen, FDA's reviewer raised concerns about suicide reports: "We note that there appears to be an increase frequency of reports of suicidality in the pediatric/adolescent patients exposed to sertraline compared to either placebo or sertraline-treated adult OCD patients."<sup>244</sup> The letter referred to the article by King et al,<sup>239</sup> which described "the development of intense self-injurious ideation and/or behavior in children and ado-

lescents with OCD who received treatment with fluoxetine." Pfizer responded in May 1996 with a suicide-related case report of suicidal behavior in children and adolescents in the Zoloft (sertraline) OCD trials.<sup>245</sup>

In October 1997, Pfizer submitted its expert report to the FDA,<sup>246</sup> providing data about two completed pediatric trials in the U.S., and two extension trials in children aged 6-12 and adolescents aged 13-17 years who were diagnosed with either depression or OCD. One a 12-week multi-center, double blind, placebo controlled study recruited 92 children to test Zoloft (sertraline) and 95 who were given placebo, of whom 67 subsequently went onto Zoloft in an extension trial. A second 51-day open label study recruited 61 children to look at the pharmacokinetics of and tolerance to sertraline after single and multiple doses. Of these 61 children 44 were depressed, and 17 were diagnosed with OCD.

During the first four weeks of this study the children's dose was increased to 200mg, a dose higher than tested in adult trials, according to the Pfizer report: "the mean maximum daily dose of sertraline was considerably higher in the paediatric studies (185mg) than in the adult OCD studies (148mg). This higher mean maximum daily dose is due to the design of the paediatric studies." [p. 31] The rationale for testing a higher dose in children remains unclear. It is also unclear why the FDA approved a "forced titration" study design,<sup>241,242</sup> which surely put children under increased stress. Serious adverse events (SAE) were defined as: "events which were fatal; life-threatening or potentially life-threatening; resulted in permanent disability; required hospitalization or prolongation of hospitalization...a drug overdose or suggested significant hazard to the patient." [p 27]

In the completed studies, there were 6 children on Zoloft who attempted suicide and a number of other children who became suicidal. Within the group of 44 depressed children, 4 attempted suicide - a rate of 9%. Suicide attempts in the main occurred within a few days of dose escalation. One of the six children who became suicidal was an eight-year-old boy who had been in the sertraline dose tolerance study for 36 days. The Pfizer 1996 suicides report states: "Patient was hospitalized for a suicide gesture, and dropped from the study. The patient #4 mutilated himself by cutting his feet with a razor blade and tying a tie around his neck. There was no previous history of self-mutilation or suicidality, although family history was significant for affective disorder (mother, maternal uncle) and suicide (maternal uncle)."<sup>245</sup> [Table 1] Pfizer's report acknowledges: "The event was attributed to study drug by the investigator."

In the same Pfizer study a 14-year old who had been receiving 200mg/day Zoloft was hospitalized on the 35<sup>th</sup> day of the study for "a moderate suicide gesture:" he is reported to have ingested "400 mg of sertraline...10 mg of lorazepam and unknown amount of organophosphate insecticide. The suicidal ideation was thought to have resolved within one day and the patient was not discontinued. The following day the patient ingested 8 g of chloral hydrate.

Nevertheless, the investigator continued the patient in the study five days later, without apparent further sequelae"<sup>245</sup> [Table 1] Pfizer's report further notes that this eight year old boy, "had been treated with methylphenidate 40mg qd for over five years, and this was discontinued immediately prior to entering the study." This would indicate that the boy was continuously prescribed psychoactive drugs since he was nine years old. To what effect, one might ask?

In May 1996 Pfizer reported 25 cases of "spontaneous reports of suicide-related behavior in children." [p. 13] But Pfizer excludes four of the cases from its report-"individuals who were not previously taking sertraline"-because, the report states, they stole the drug for the purpose of suicide or abuse. [p. 13] The 1997 report refers to 21 SAEs in 16 patients in the OCD studies (total 220 children on Zoloft) [p. 28] and in the non-OCD studies (38 children), there were 11 SAE in 7 patients on Zoloft (18.4%). "These included three reports of suicidality, and single reports of malaise, intentional drug overdose, medical/surgical...aggressive reaction, aggravated depression..."[p. 29] According to Pfizer, "The adverse events most frequently associated with discontinuation were psychiatric symptoms, most commonly agitation." [p. 21] Children (6 to 12) on Zoloft were especially prone to agitation: 15.1% (compared to 1.9% on placebo); 10.3% of adolescents (13 to 17) became agitated (compared to 2.4% on placebo). [p. 23] Pfizer reports: "there were no serious adverse events reported in the 95 patients in the placebo group." [p.28] It is of significance that the children and adolescents were not monitored for suicidal behavior, the report is based on "spontaneous" (i.e., voluntary) reports with "minimal information in most reports about the cases."<sup>245</sup> [p. 13]

Pfizer acknowledges that "most reports do not contain sufficient information to allow one to draw conclusions or characterize the events." [p. 17] Neither do "spontaneous" reports reflect the number or severity of the events. It is troubling that despite concern by some FDA experts the agency has not required careful monitoring of children who are subjects of clinical trials testing psychotropic drugs. And the academic literature stemming from these studies evade the crucial issues of concern by failing to report the actual scope and nature of the serious adverse events suffered by children and adolescents in the Zoloft trials. The published reports exclude adverse events that occurred at a frequency less than 10%.<sup>242,243</sup> In this way the reports include only common but less severe adverse events such as, headache, insomnia, nausea, dizziness, and diarrhea, but exclude serious, potentially life threatening adverse events that led some children to drop out. In particular, restless agitation (i.e., akathisia), occurring in 15.1%. Neither do the published reports reveal that in the depressed group in the children's trial, suicidal attempts occurred at a rate of 9%.

These published reports demonstrate the validity of Klassen's finding.<sup>237</sup> It is unclear what SAE disclosure criteria, if any, are being followed in published peer reviewed reports in the scientific journals. Failure to report all seri-

ous adverse findings undermines the integrity of the scientific literature and, more importantly selective reporting misleads clinicians who then mislead patients and families to believe the drugs are benign when they are not. Those who skew clinical trial reports may be accused of complicity in keeping clinicians uninformed, and unprepared, thereby undermining the safety of patients prescribed SSRIs.

#### **FDA's failure to require drug safety warnings:**

Prozac (as has been shown above) generated more adverse drug reaction reports than any drug in America,<sup>191</sup> including 2,000 reports of suicide deaths linked to Prozac which, by the agency's own calculations reflects but a fraction of the likely number of suicides.<sup>199</sup> FDA documents obtained under the Freedom of Information Act show that by 1990 the agency's expert analysts had serious concerns about the frequency of "suicidality" (suicide acts) reports. However, internal Lilly documents reveal that high-level FDA officials personally assisted Lilly to overcome calls for a drug label warning that would have alerted physicians and the public about life-threatening treatment-emergent risks.<sup>247</sup> The chief FDA epidemiologist who reviewed Lilly's adverse drug reaction analysis, concluded: "Overall, the analysis presented by the firm (i.e., Lilly) had several shortcomings which should be noted. In the meta-analysis of suicidality from [investigational new drug] IND trials, 76 fluoxetine cases were excluded from analysis because patients were lacking comparative controls."<sup>248</sup>[p.4]

Dr. Bruce Stadel,<sup>249</sup> expressed strong reservations about such underreporting: "It is inappropriate in a safety analysis to exclude such a large proportion of cases. A fluoxetine suicidality rate should be computed for the uncontrolled studies and compared to the rate for the controlled studies..." Lilly prefaced its review with an acknowledgment that "these trials were not designed for the prospective evaluation of suicidality. In these trials, patients with current suicidal ideation were excluded..." Lilly further acknowledged, "The capacity of these trials to identify and describe the quality and intensity of suicidality was low."<sup>248</sup> FDA's Acting Director, Office of Epidemiology and Biostatistics, Dr. Stadel, made recommendations to remedy the trials' low capacity to identify suicidality. He called for case-control analyses to identify pre-treatment risk factors-to save lives. Instead of a detailed case-control analysis, Lilly scientists led by Dr. Beasley,<sup>231</sup> conducted a study whose design was dictated by the need to assert the drug's safety. Ultimately, the responsibility for determining what safeguards drug companies must provide, lies with the FDA. It would appear that high-level agency officials put the financial interest of the companies above the need to take preventive measures to decrease the risk of suicide. Lilly submitted the Beasley study findings as evidence of the drug's safety. In 1991, on the basis of that study, FDA's Psychopharmacologic Drug Advisory Committee,<sup>250</sup> chaired by Dr. Daniel Casey, dismissed the significance of the large number of suicide reports from physicians' case accounts by claiming they were inspired



by the Teicher article,<sup>251</sup> as if published clinicians case reports had no merit. Lilly used this committee report to claim it "proved" Prozac is not to blame, FDA has never initiated a study to find the cause or remedy against treatment emergent suicide events, or required the company to do so-even as its own director of epidemiology had so recommended in 1990.<sup>249</sup> Lilly's internal documents that were uncovered during litigation procedures reveal that the company knew all about the suicide risk and took measures to mask the evidence, rather than protect the patients. Even after these company documents were revealed in court, FDA has failed to investigate and failed to issue a warning in the package label to alert doctors about the risk, as did the German and British agencies. Event though Pfizer acknowledges that "it is well known that spontaneous reports are not a good indication of the true frequency of events,"<sup>245</sup> [p. 17] FDA does not even require investigators of psychotropic drugs to monitor clinical trial subjects for suicidal signs.

It was further revealed in confidential documents that Lilly secretly paid \$70 million for patent rights to a new (improved) version of Prozac.<sup>220,224</sup> The new, improved Prozac patent states that it decreases adverse side effects including: "nervousness, anxiety, insomnia, inner restlessness (akathisia), suicidal thoughts, self mutilation [and] manic behavior."<sup>252</sup> Is this then an oblique acknowledgment that akathisia, suicidal thoughts and self-mutilation have been associated with "the old" Prozac? Unless these life-threatening side effects were a problem associated with "the old" Prozac they would surely not be listed to denote an improvement with the new Prozac. It is difficult to fathom why the FDA has been silent on the issue of life-threatening risks even when it became known that the drug was being prescribed for children. Despite concerns about its safety and unproven effectiveness for children, FDA approved Prozac for children with depression and OCD on January 3, 2003.<sup>253</sup> In 2000, Lilly had been the first pharmaceutical company to gain a six-month patent extension for Prozac under FDAMA which industry analysts' estimate will earn Lilly \$831 million.<sup>254</sup> FDA's decision lends an air of legitimacy to widespread inappropriate prescribing of mood altering drugs for children of all ages.<sup>104,120,119</sup> FDA appears to have ignored the potential serious risks, the absence of any empirical evidence to support the use of such drugs in young children, and the preponderance of negative findings that do not support the efficacy of antidepressant drugs in children.

#### **The morality of exposing children to risks in nontherapeutic experiments:**

Children have often been the victims of harmful, speculative, even abusive experiments conducted without regard for their humanity. In 1942, ninety-eight "schizophrenic" children, aged four to eleven were electro shocked twice daily for twenty days in a row at New York City's Bellevue Hospital.<sup>255</sup> Bellevue psychiatrist, Dr. Lauretta Bender, presented a report about this "successful" experiment, although years later other investigators who followed up

found several of the children had become violent and suicidal.<sup>256</sup> In 1955, Dr. Bender published a case report of a toddler (not yet three years old) who she had claimed to have "successfully" put through twenty-shock "treatments" at Bellevue.<sup>257</sup> The abuse of children in psychiatric research did not end in 1942. The abuse today is likely to be chemical.

As noted above, federal regulations for the protection of children were adopted in the wake of revelations about the Willowbrook experiments exposed mentally retarded children to hepatitis to afford researchers an opportunity to study the course of hepatitis.<sup>4</sup> As discussed earlier, federal regulations impose restrictions on the use of children in medical experiments involving greater than minimal risk. Thus, research involving "minor increase over minimal risk" and no prospect of direct benefit is permitted only if it is "likely to yield generalizable knowledge" which is of "vital importance for the understanding or amelioration of the subject's condition."<sup>51</sup> [45 CFR 46.406] However, as the cases described in this paper demonstrate, the regulations are inconsistently interpreted by IRBs that cannot be relied upon to serve the best interests of the child subjects. Those seeking to recruit children for experiments that expose them to risks without a direct benefit have argued that parental consent is sufficient to legitimize the exposure of children to risk.<sup>267</sup> However, the presidential Advisory Commission on Human Radiation Experiments (ACHRE) concluded otherwise after examining a 30-year record of experiments involving children. The ACHRE Final Report<sup>258</sup> documents a long litany of experimental abuse of children in government sponsored radiation experiments, sometimes with parental consent. Therefore, the ACHRE panel emphasized the need to protect children even to the point of overriding parental authority:

Where the research does not offer any prospect of benefit to the child, however, the legitimacy of the parent as authorizer is less clear. . . Respect for the authority of parents to make decisions for their children and otherwise control their children's lives is not without bounds. The law recognizes several exceptions, designed primarily to protect the child from what society at large considers to be unacceptable or unjustifiable harm or risk of harm. . . In the context of research, the question arises of whether a parent has the authority to permit a child to be put at risk of harm in an experiment from which the child could not possibly benefit medically. In this case, the child is to be used as a means to the ends of others.<sup>258</sup>[Chapter 7, online]

The ACHRE Commission clearly stated that such exploitation of children could not be rendered morally acceptable. The ACHRE report and the Commission's deliberations reflect a moral frame of reference guided by the reflection of prominent ethicists, such as Paul Ramsey, who in 1974 passionately argued against the degradation of children as experimental subjects.<sup>259</sup> The same princi-

pled moral barometer informed the British Medical Research Council opinion<sup>260</sup> and US court rulings that have similarly affirmed the right of children to be protected from nontherapeutic research that offers them no direct benefit.

In 1995, Justice Edward Greenfield struck down New York State's mental health research regulations allowing surrogate consent to nontherapeutic research, stating: "Parents may be free to become martyrs themselves. But it does not follow they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves."<sup>261</sup>

#### Case 9: Babies exposed to lead paint poison:

From 1992 to 1995, healthy babies and toddlers in Baltimore were exposed to lead paint dust in a clinical trial for the purpose of determining the effectiveness of varying degrees of lead paint abatement. The experiment was sponsored by the Environmental Protection Agency and the State of Maryland; it was conducted by researchers at the Kennedy Krieger Institute (KKI) of Johns Hopkins University; and came to light when two lawsuits were brought before the Maryland Court of Appeals after being dismissed by a lower court.<sup>262</sup> During the experiment, researchers drew blood samples from the children and recorded the rising level of lead in their blood. The *Washington Post*<sup>263</sup> reported that in seven months, lead levels for three of the children rose from 6 to 21 micrograms (Myron Higgins), from 9 to 32 micrograms (Ericka Grimes), and from 10.7 micrograms to 24 (for Charnice Martin).

In its strongly worded ruling, on August 6, 2001, the Court of Appeals noted that the researchers did nothing to intervene even as the lead in the children rose to hazardous levels. KKI lawyers argued that the institute bore no legal obligation to warn the parents about the risks to which the children would be exposed—namely that exposure to lead dust could reduce the intelligence quotient (IQ) and cause mental retardation. KKI lawyers argued that federal regulations (45 CFR 46) do not apply, claiming that the regulations "only require to inform research subjects of the risks inherent in the interventions to which the researchers intend to expose them."<sup>264</sup> They made the preposterous claim that the researchers were only engaged in "passive data collection" not in the actual intervention process, therefore they should be exempted from federal regulations. The institution's lawyers further argued that exposing children to lead poison does not fall under "biomedical research" and does not, therefore, come under federal regulations. And they argued that the signed consent forms are not binding contracts, that KKI had no duty to report the elevated lead levels to families.

The Court was especially critical of the Johns Hopkins IRB for "abdicating [its] responsibility" toward protecting the subjects—as required under federal regulations<sup>30</sup>—by suggesting "to the researchers a way to miscast the characteristics of the study in order to avoid the responsibility

inherent in nontherapeutic research involving children." [p. 5] The Court further criticized the "IRB's improper attempt to manufacture a therapeutic value" for this experiment when "there was absolutely no such value in the research" for the children. [p. 84] Indeed, the Court pointed out, the success of the experiment was "to be measured, in substantial part, by the degree to which the research environments cause the absorption of poisons into the blood of children." [p. 84] The decision against the Kennedy Krieger Institute unequivocally affirmed the pre-eminence of the child's best interest standard, stating:

whatever the interests of a parent, and whatever the interests of the general public in fostering research that might, according to a researcher's hypothesis, be for the good of all children, this court's concern for the particular child...over-arches all other interests....It is, simply...not in the best interest of any healthy child to be intentionally put in a nontherapeutic situation where his or her health may be impaired, in order to test methods that may ultimately benefit all children.

The decision puts the medical research establishment on notice that the use of children in nontherapeutic experiments for the good of other children is unacceptable. The Court also held that parental consent to children's participation in potentially hazardous experiments is invalid—"even if it can be argued it is for the greater good" [p. 79]. Furthermore, the Court affirmed the moral and legal responsibility of parents, the government, researchers, and institutional review boards to protect children from health risks in non-therapeutic experiments. And affirmed that the burden of providing ethical justification for conducting research on young children rests with those who propose the trials—it is they who must bear responsibility for protecting the welfare of the children.

This resounding decision by Maryland's highest court, affirmed a child's right not to be exposed to any risk above minimal in nontherapeutic experiments. Research stakeholders, with the assistance of advisory committees have embarked on a strategy to eliminate the distinction between therapeutic and non-therapeutic research and thereby circumvent federal restrictions on pediatric research: Thus, a letter to the FDA states: "NHRPAC is disturbed to note that this proposed amendment reinstates the illogical distinction between therapeutic (beneficial) and nontherapeutic (nonbeneficial) research."<sup>265</sup> Unlike the vaguely worded federal regulations, which leave decisions about what constitutes "minimal risk" to the discretion of IRBs (who are employees of the institution), the Court's prohibition against conducting nontherapeutic research on children if it poses any risk of harm was explicit. This explicitness caused much consternation within the research establishment. Johns Hopkins and University of Maryland officials lobbied Maryland legislators to pass a law to legitimize nontherapeutic experiments on children and cognitively impaired individuals.<sup>266</sup> The

Association of American Medical Colleges, Association of American Universities joined these institutions in filing amice curiae briefs asking the Court to reconsider.<sup>267</sup> One human rights watchdog organization filed an Amicus Curiae brief in support of the Court's decision.<sup>268</sup> It appears that the primary, if not the only concern for the research stakeholders is the possibility that research grants could be jeopardized.<sup>269</sup>

#### Case 10: Spinal Taps for Science:

In 1996, F. Xavier Castellanos,<sup>47</sup> and a team of child psychiatrists from NIMH and three other institutions<sup>270</sup> reported about a nine-week, cross-over, multiple drug experiment they had conducted on 45 boys, aged six to eleven. The investigators indicated they were replicating their own previous research.<sup>271</sup> The children in the replication study had been diagnosed with ADHD and other equally controversial behavioral disorders, including "conduct disorder", "oppositional disorder", and "mild over-anxious disorder". The purpose of the experiment was to test the effect of stimulant drugs (methylphenidate, dextroamphetamine, compared to placebo) on the cerebrospinal fluid (CSF) levels of dopamine (HVA), norepinephrine (MHPG), and serotonin (5-HIAA) and to find a correlation between HVA levels and hyperactive behavior. A subset of 16 boys was also tested on magnesium pemoline.

In the course of the experiment, the children were subjected to pain and risks of spinal taps for nontherapeutic experimental purposes. The investigators reported that originally, 54 children had been enrolled in the experiment, but two who initially agreed to participate later refused the lumbar puncture, a requirement of the study protocol.<sup>47</sup>[p. 126] Another child was excluded from the study when he was diagnosed with Tourette's disorder. The investigators reported that two children who had previously undergone lumbar puncture "could not be located for reanalysis" and four were omitted from the analysis because cerebrospinal fluid (CSF) was "unobtainable" from them.<sup>272</sup> It is not clear why the children had to undergo lumbar punctures since HVA is excreted in urine and could have been measured another, less painful way.

The experiment can be faulted on several methodological grounds:

- (1) Those who carried out the experiment, according to their own admission, had no criteria for evaluating whether "high HVA" levels (in some subjects) were within the normal range of HVA levels.<sup>273</sup> Three earlier studies, conducted by other investigators, did not support consistent standards for CSF HVA abnormalities in persons "diagnosed" with ADHD.<sup>274</sup> If the expected HVA range was unknown, any conclusions derived from measuring HVA levels in study participants could not be extrapolated beyond the subjects of the experiment, and therefore of no scientific value.
- (2) There was no control or comparison group for the

study.<sup>275</sup>

(3) 80% of the study's subjects had already been exposed to stimulant drugs before the experiment and, as the experimenters themselves recognized, the residual effect was likely to confound their findings.<sup>276</sup>

(4) "Due to technical problems", six subjects were deemed "outliers" and were, therefore, deleted from the analysis of MHPG values.<sup>47</sup> [p. 128]

(5) There were four different experimental treatments. Subjects had been divided into groups that received three stimulant drugs or a placebo-- but the procedures that were followed were inconsistent. The investigators did acknowledge that "precise comparisons are not possible due to differences in methodology, subjects, and ages,"<sup>47</sup> [p. 128] claiming their results were consistent with other published pediatric studies.

(6) Ratings of the behavior of the study subjects were made by teachers and parents. It is not possible to conclude anything about the validity of their ratings.<sup>277</sup>

(7) The investigators' statements of findings are sometimes contradictory: e.g., on page 133 of their report, they note, "This is the first finding of a significant direct relationship between baseline CSF metabolite levels and subsequent behavioral response to medications." However, one page earlier they had said, "We did not find significant correlations between MHPG behavioral ratings of severity on placebo or of improvement on medication." And on page 128 they stated, "Improvements on the continuous performance test (CPT) did not correlate significantly with monoamine metabolite levels for any stimulant" and neither did physician scores "correlate with metabolite levels for either medication." [p.128]

(8) The investigators state, without explanation, that "some subjects worsened on medication compared to placebo." [p. 128] One would want to know, how many subjects worsened, a description of "worsened" behavior, and whether they recovered?

The experiment suffered from serious ethical, methodological and interpretive problems. In this experiment young children were exposed to considerable pain and unjustifiable, "greater than minimal risk," to test a hypothesis, not to test a potential therapeutic treatment. The investigators did not demonstrate that the information they sought was either in the children's best interest or "unprocurable by other means."<sup>1</sup>

#### Case 11: Fenfluramine "challenge" Experiment for Science:

In 1997, the *Archives of General Psychiatry* published a report Dr. Daniel Pine<sup>278</sup> and a team from the New York State Psychiatric Institute (NYSPI) about a fenfluramine "challenge" experiment that had been conducted on 34 six-to eleven- year-old African American and Hispanic boys. The children were drawn from a sample of a larger study involving 126 brothers who were deemed "at risk" of following in the footsteps of their older brothers who were incarcerated juvenile delinquents. The investigators

claimed that "there is evidence" of a correlation between reduced serotonin activity and aggressive behavior. They hypothesized that by measuring the boys' biochemical responses to fenfluramine they would be able to replicate earlier findings and find a predictive biological marker predisposing the children to violence. The published report indicates that the children were required to follow a special diet for four days, to fast for 18 hours before they were to swallow fenfluramine ("challenge"), and they were to have an intravenous catheter inserted in their arm, which would remain for more than five hours, during which time blood would be drawn. The investigators justified the risks and discomfort that the children would bear, by stating: "Research on the relationship between adverse rearing and serotonin may enhance understandings of the association between serotonin and aggression across development." [p. 841]. [Emphasis added] Parents were paid \$125 and the children received \$25 dollar gift certificates to Toys 'R Us.<sup>279</sup>

This experiment encapsulates many of the flaws in the current human research review, approval and oversight system, by demonstrating institutional failings. First, although federal regulations prohibit the use of children in research involving "greater than minimal risks" if there is no potential benefit for them,<sup>51</sup> four prominent institutional review boards approved this speculative, nontherapeutic experiment. The members of those review boards saw nothing wrong with an experiment that would expose children to greater than minimal risks, discomfort, trauma, and label them as "predisposed to violence." Nor did they appreciate the potential harm that may be caused the children from being labeled henceforth with a psychiatric diagnosis linked to aggression.<sup>280</sup>

Second, fenfluramine carries far greater risks than "minimal risk"-it carries the risk of neurotoxicity,<sup>281</sup> and it was later learned, the risk of heart valve damage. As early as December 15, 1993, neuroscientists had warned the FDA not to approve fenfluramine or its combination form, fen-phen (trade name: Redux).<sup>282</sup> They pointed out that, "Redux had been shown to cause brain damage in animals and might do the same in humans by eroding the body's supply of serotonin." In 1996, Dr. Muldoon and investigators at the University of Pittsburgh reported that a single dose of fenfluramine had caused adverse side effects in 90% of the normal human subjects who reported fatigue, headache, lightheadedness, and difficulty in concentrating.<sup>283</sup> In September, 1997, the drug was recalled after FDA had received at least 100 reports of heart valve damage and news of a much higher than expected percentage of abnormal cardiograms. In its withdrawal announcement FDA stated: "Approximately 30% of the patients that were evaluated had abnormal echocardiograms, even though they had no symptoms. This is a much higher than expected percentage of abnormal test results."<sup>284</sup>

Third, the children did not display any aggressive behavior at the time they were recruited for the experiment. The children could not, therefore, be regarded as having a condition that could be helped by the study.

Indeed, the study was not designed to provide any benefit for either aggressive or non-aggressive children-it was a wholly nontherapeutic experiment. Aside from the experimenters' very questionable hypothesis<sup>285</sup> - i.e., a biological disposition to aggression and conduct disorder-the experiment put the children at greater than minimal risk but offered no conceivable benefit to the children tested. Further, given what was already known to neurologists about fenfluramine, the experiment clearly violated medicine's first principle, "First, do no harm," not to mention existing federal standards for approvable experiments involving children.<sup>51</sup> It would seem that everyone with a duty to protect the children's best interest had failed to act in their best interest.<sup>67</sup>

When news of the fenfluramine "challenge" experiment hit the media,<sup>286</sup> it was greeted with public condemnation, followed by several congressional hearings,<sup>287</sup> a lawsuit and a federal investigation.<sup>288</sup> Public reaction across the country revealed a conflict between the principled moral values that guide the perspective of the citizenry and the utilitarian ethics that drive the stakeholders in the research enterprise. The citizenry's moral barometer does not sanction the use of children as means toward an end in experiments not intended for their benefit but rather to simply further research goals. By contrast, the research stakeholders and gatekeepers have given the practice their seals of approval.

Investigative reporters uncovered additional ethical / legal violations-such as, violation of privacy and confidentiality of the criminal justice system.<sup>289</sup> The names of the 126 boys had been obtained from the New York City Parole Department because of their brother's involvement with the justice system. None of those entrusted with protecting research subjects-the researchers, the IRBs or the Office of Protection from Research Risks (OPRR), now called the Office of Human Research Protections (OHRP)-had examined the validity of the dubious scientific rationale of the experiment. They also failed to notice the absence of an ethical justification for putting children at risk of harm, the absence of any potential benefit to the study subjects, or its discriminatory selection criteria (in violation of The Belmont Report<sup>5</sup> justice requirement for equitable distribution of risks and benefits), and coercive recruitment procedures. Dr. Jack Gorman (at the time) Deputy Director of the research center stated: "The New York State Psychiatric Institute has carried out its research of patients professionally, ethically and appropriately, and we stand by our statement."<sup>290</sup> The researchers argued that although the children had no diagnosable condition-an essential requirement for experimentation under federal regulations<sup>51</sup>-they were "at risk" of a condition. The "condition" it was claimed they were "at risk" of having, was "predisposition to violence"-a condition neither defined in medicine nor known to be ameliorated throughout the history of medicine by medical treatment. The argument is specious. The logical contortions of such reasoning appear to have been employed for the purpose of addressing the federal prohibition against the use of children in nonthera-

peutic experiments that pose greater than minimal risks. It would appear that those involved in designing and conducting the experiment, and those who reviewed and approved it, believed the children were suspects ("at risk") by virtue of their kinship relationship with adjudicated juvenile delinquents. Dr. John Oldham, Director of NYSPI and (at the same time) Chief Medical Officer of the State Office of Mental Health told the *New York Times*, "the experiments may provide information on the biological basis of aggressive behavior...we don't have a lot of treatment methods for them. If we could learn how to intervene, it could be enormously valuable."<sup>291</sup> However, the experiment was not designed to "learn how to intervene," it was designed to test a hypothesis about the predictability of violent behavior on the basis of a biochemical response to fenfluramine. *United Press International* reported that while conceding that the experiment had no medical value, Dr. Gorman defended it by stating "all attempts to find solutions to serious mental health problems begin with research like this."<sup>292</sup> It is unclear whose mental health problems Dr. Gorman was referring to. When questioned about the racial composition of the subjects, he claimed it reflected the Washington Heights neighborhood in which NYSPI is situated.<sup>285</sup> But at least one of the boys in the experiment lived with his parents in Brooklyn.<sup>289</sup>

None of the boys could be shown to have the condition in question at the outset of the experiment. By invoking an "at risk" rationale, all those subjects included in the experiments could be *induced* to demonstrate a tendency to get the *hypothesized* condition when subjected to fenfluramine "challenge." However, that argument is flawed because it presupposes an underlying "condition" which the experiment set out to prove. The argument also presupposes—without evidence—a causal relationship between serotonin levels (affected by fenfluramine) and the tendency toward violence, now or in the future. Without evidence of such a causal relationship, it cannot legitimately be argued, that the experiment could benefit the child participants now or in the future. Since the experiment posed greater than minimal risk, provided no prospect of direct benefit to the child-subjects who were not ill, and was not designed "to yield generalizable knowledge of vital importance for the understanding or amelioration of the subject's condition," it was unapprovable under federal regulations.<sup>51</sup>

OPRR accepted the "at risk" argument made by the New York State psychiatric research establishment.<sup>293</sup> The acceptance of this specious argument reflects a radical shift in federal policy (see discussion above). Both the psychiatric research establishment and the pharmaceutical industry seized upon OPRR's precedent in legitimizing the fenfluramine experiment to inaugurate ever more aggressive experiments on children. It seems astonishing that the reviewing committees and the National Institute of Mental Health that funded them approved these painful, wholly non-therapeutic experiments. A moral schism clearly separates the culture of utilitarian ethics invoked by researchers who design, approve and conduct nontherapeutic experi-

ments on children, and the principled values that informed the deliberations of the president's Advisory Commission on Human Radiation Experiments (ACHRE).<sup>258</sup> Since FDAMA, more children have been subjected to nontherapeutic "challenge" experiments on the basis of unproven hypotheses, simply by conjecture that they were "at risk" of a condition.<sup>294</sup> FDAMA paved the way for the pharmaceutical industry to launch aggressive marketing strategies: early prevention of hypothesized conditions in children who are classified "at risk." The transition demonstrates the ease with which the self-regulating system of research protection can be bent to accommodate the needs of research stakeholders. It fails to protect children from questionable experiments.

### Safety issues antipsychotics-olanzapine (Zyprexa):

In 1996, FDA approved Eli Lilly's drug, olanzapine (Zyprexa), for treatment of adults diagnosed with schizophrenia. Olanzapine is one of a so-called class of atypical neuroleptics (antipsychotics) whose benefits are debatable, but Lilly's marketing approach followed the Prozac formula.<sup>295</sup> Olanzapine was promoted as the "new wonder drug," "a weapon against schizophrenia," its promoters claimed it has "substantial advantages" over its predecessors, such as greater safety and effectiveness, with fewer side effects. Its high price—between \$5,000 and \$10,000 a year, depending upon dose—and aggressive marketing quickly made it the best selling antipsychotic drug on the market. In 1998 sales reached \$1.28 billion in the U.S.,<sup>296</sup> and in 2002, sales reached \$3 billion.<sup>297</sup> However, olanzapine induces profound changes in the central nervous system with demonstrable physical and neurological impairments.<sup>298</sup> Dyskinesia, the disfiguring involuntary movement disorder is a side effect of olanzapine and all the other typical and atypical antipsychotics, except clozapine, which has its own problems. In 1998, the *Boston Globe* reported that while it was still in clinical trials, before the drug was approved by FDA, olanzapine had been linked to serious, in some cases life-threatening side effects requiring hospitalization in 22% of the adults on whom it had been tested.<sup>299</sup> According to FDA data obtained subsequent to a Freedom of Information Act request by the *Globe*: there had been 22 deaths, 12 of which were suicides; the drop-out rate during 6-week clinical trials had been 65%; and in an extended (one year) trial, the drop out rate had been 83%.<sup>299</sup>

Among the reported severe adverse side effects experienced by the subjects during clinical trials of olanzapine: cardiovascular complications (10% to 15%); acute weight gain (50%), an effect that signaled an increased risk for diabetes. Parkinson-like motor impairment (11.7%); and akathisia (restless agitation) (7.3%).<sup>300</sup> From the discussion above, it has been strongly suggested by senior psychiatrists at premier research institutions and in internal Eli Lilly documents that akathisia is the likely catalyst for suicidal and homicidal ideation and eruption.<sup>221</sup> The inordinately high suicide rate in the olanzapine trial may be a consequence of drug-induced akathisia (agitation). After

the drug's approval, other severe adverse effects surfaced. These included new onset diabetes<sup>301</sup> within three to six months of initial use of olanzapine, liver abnormalities, severe akathisia,<sup>302</sup> induced mania,<sup>303</sup> seizures, hyperglycemia (elevated cholesterol),<sup>304</sup> severe weight gain,<sup>305</sup> tardive dyskinesia (TD),<sup>306</sup> a debilitating disfiguring pathological disorder that may be irreversible, and the potentially fatal, neuroleptic malignant syndrome.<sup>307</sup> The Australian Adverse Drug Reactions Advisory Committee had received 18 reports of white blood cell disorders (neutropenia), 15 reports of seizures / convulsions, and 7 reports of neuroleptic malignant syndrome.<sup>308</sup>

The severe adverse side effects reported during a brief clinical trial of olanzapine, the high drop out rate during that brief period, coupled with a growing body of post marketing evidence of serious adverse effects—some leading to debilitating chronic conditions, such as diabetes—as well as evidence showing that chronic exposure to antipsychotics may have produced greater harm than benefit,<sup>309</sup> should have dissuaded doctors from prescribing the drug experimentally for children. Of particular concern when children are involved are the potential long-term risks. Indeed, FDA's conditional approval of olanzapine for manic episodes in adults was limited to "the short-term treatment of acute manic episodes associated with bipolar disorder."<sup>310</sup> This conditional short-term approval lends support to suspicions that the drug is likely to produce irreversible consequences with prolonged use.

Despite such concerns, soon after olanzapine gained FDA approval for adults with schizophrenia, five children aged six to eleven were recruited for clinical trials. According to the published report, the children recruited for olanzapine trials by investigators at the University of California—Los Angeles were not even diagnosed as having schizophrenia; they were diagnosed as having a variety of questionable psychiatric disorders, including ADHD,<sup>311</sup> a condition whose psychiatric validity has never been established. (See discussion above) According to the published report, all the children who were given olanzapine experienced adverse effects, including sedation, weight gains of up to 16 pounds, and akathisia (extreme agitation). None of the children were helped by olanzapine and the trial was terminated less than six weeks after it had begun. Since nothing in the published report provides a medical justification for prescribing an antipsychotic drug for these young children, they were exposed to the drug's serious risks for non-medical reasons. It seems likely that the decision to test olanzapine in the children was influenced by enormous financial incentives—additional revenues from a six-month patent extension under FDAMA.

#### Case 12: An association between olanzapine (Zyprexa) and new-onset diabetes:

Soon after its marketing, case reports linked olanzapine to diabetes. "Diabetes affects virtually every tissue of the body.... Life expectancy for people with diabetes averages 10-15 years less than that of the general population."<sup>312</sup> Until the introduction of the atypical antipsychotics, cloza-

pine (Clozaril) and olanzapine (Zyprexa), the condition was rare in children and adolescents. At the August 2001 meeting of American Psychiatric Association, Dr. Frank J. Ayd,<sup>313</sup> an internationally renowned psychopharmacology expert, and editor of the *International Drug Therapy Newsletter*, presented findings of his review of the literature for atypical antipsychotics. He found a "startling" association between initiation of treatment with olanzapine and new-onset diabetes in adolescents:

New-onset diabetes after antipsychotic treatment initiation is startling, since the use of atypical antipsychotics has become the first line of treatment for schizophrenia...Twenty-six case reports were analyzed, of which 14 reports of diabetes, diabetic ketoacidosis (DKA) or worsening diabetic blood glucose control after initiation of olanzapine were found. Five (36%) of these patients developed DKA. Seventy-nine percent of the patients were compelled to discontinue their antipsychotic. Eighteen percent of the patients who discontinued their medications required long-term insulin; 18% required long-term oral hyperglycemic treatment.

These disturbing findings have been confirmed by other scientist.<sup>314</sup> In November 2001, Dr. Elizabeth Koller, Saul Malozowski,<sup>315</sup> of FDA's Center for Drug Evaluation Review (CDER) and Dr. P. Murali Doraiswamy of Duke University analyzed FDA's MedWatch adverse event reports and reported their findings in *JAMA*. They found a causal association between olanzapine (Zyprexa) and diabetes, *ten times higher* than in the general population. In 2002, a team of researchers from the Caro Research Institute<sup>316</sup> reviewed the patient database of a Quebec clinic for a two-year period (January 1, 1997 to December 31, 1999) and reported a startling finding. Of 33, 946 patients who had taken either olanzapine (19,153) or another atypical antipsychotic drug, risperidone (14,793) within just 90 days of exposure to olanzapine 319 patients (1.7%) developed diabetes, and 217 patients developed diabetes while on risperidone. Only those patients who had no prior history of diabetes were included in the review. These findings put the risk of diabetes for patients prescribed olanzapine at 1.7% within 90 days.

Until now, diabetes was a disease of the elderly. Worldwide sales of drugs to treat diabetes reached \$8.1 billion in 2001. With an annual growth of 19%, IMS Health, the leading market research firm tracking the global pharmaceutical industry, estimates that the market for diabetes medications could exceed \$20 billion by 2006.<sup>317</sup> Eli Lilly, the manufacturer of olanzapine, is a leading producer/ distributor of diabetes treatment products. An expanding patient base can guarantee strong sales for years—if not decades.

Is it possible that one drug is being used to cause a chronic condition that will require long-term "treatment" until death?

### Marketing "schizophrenia prevention:"

Before a physician can legitimately prescribe pharmacological interventions for the prevention of a medical condition, such as psychosis, there are at least 5 methodological issues that should be addressed:

1. The predictive validity of the screening instruments used.
2. The quality of the condition's diagnostic validity.
3. The presumption that minor or transient symptoms are specific predictors of later full-blown psychosis and
4. The validity of the assumption that drugs used to treat manifest "schizophrenia" would be best for its prevention.
5. A favorable risk/ benefit ratio between the intervention and non-intervention.

Psychiatric research has consistently failed to meet those requirements—especially in pediatric research. Before considering ethics and scientific validity of the so-called, "schizophrenia prevention experiment," a brief review of the adverse results of decades of schizophrenia treatment with antipsychotic drugs may be instructive. Robert Whitaker makes a compelling argument in *Mad in America* that while patients, their families, and the public had been reassured with false claims about the safety and efficacy of treatments, the therapies imposed on patients diagnosed with schizophrenia have mostly exacerbated their condition, rather than improved it, while producing iatrogenic pathology.<sup>318</sup> Historically, the profession has disqualified the perspective of patients diagnosed with schizophrenia; the adverse effects of treatment on their lives have been largely ignored. In *The Creation of Psychopharmacology*, Dr. Healy<sup>223</sup> notes, "As they [psychiatrists] became familiar with the idea that neuroleptics could cause dystonias and dyskinesias and that these were drug induced rather than hysterical, they stopped worrying about them." [p. 245]

Whitaker documents how one after another experimental brain disabling "treatment" had been declared "therapeutically" successful by the profession. Evidence of their success was demonstrated, not by patients getting well, but by carefully crafted reports in the professional literature, at professional conferences, and in the popular press. The reality was that the therapies damaged the brain's frontal lobes, which is the distinguishing feature of the human brain. The neuroleptic drugs used since the 1950s "worked" by hindering normal brain function: they dimmed psychosis, but produced pathology often worse than the condition for which they have been prescribed—much like physical lobotomy which psychotropic drugs replaced. But for forty years psychiatry denied that these drugs caused debilitating neurological, cognitive and motor impairment (Parkinson's symptoms).<sup>320</sup> Indeed, patients, families, the public and even psychiatrists in

training had been misled to disregard debilitating side-effects produced by the drugs and to focus on the dimming of "positive" (psychotic) symptoms. Psychiatry steadfastly denied the emergence of disabling drug-induced side effects such as tardive dyskinesia (TD), the second most pervasive drug-induced pathology. The 1985 *Clinical Handbook of Antipsychotic Drugs* declared, antipsychotic drugs "are among the safest agents in the medical armamentarium," adding, "even if a mild TD develops, it is not a heavy price to pay for relief from the suffering..."<sup>321</sup> In fact, TD is a debilitating (often irreversible) condition caused by neurological damage, characterized by disfiguring involuntary muscle movements of the face and neck. Recent research findings corroborate earlier reports linking TD to a deterioration of cognitive functions.<sup>322</sup> It is estimated that TD afflicts 40% to 60% of patients taking neuroleptics over time its incidence rate increases with each year.<sup>323</sup>

In 1986 Drs. Brown and Funk wrote a seminal article about the politics of denial,<sup>324</sup> "there was considerable avoidance to recognizing TD" (p. 121) and researchers deliberately selected data and study methods that would minimize the results. (p. 119). In his widely read, 1983 book, *Surviving Schizophrenia*, Dr. E. Fuller Torrey continued to assure families, "antipsychotic drugs are among the safest group of drugs known."<sup>325</sup> But those assurances are belied by patients' worsened condition and drug-induced pathologies that added insult to injury and shortened their lives.<sup>326</sup> Another drug-induced pathological effect to emerge with the use of neuroleptics is extreme restlessness, agitation (akathisia), estimated to occur in 8 to 76 percent of patients, with 20 to 30 percent being a conservative estimate.<sup>327</sup> This drug-induced action may explain why violent acts by patients with schizophrenia have increased.<sup>328</sup>

Just as the FDA has failed to alert clinicians about the risk of suicide for some patients taking SSRI antidepressants, the agency failed to issue an alert to psychiatrists about the risk of TD even as NIMH findings by its own investigators showed a 100% increase of incidence of TD between 1960 and 1980.<sup>329</sup> Brown and Funk<sup>324</sup> report that it was only when drug manufacturers were confronted with lawsuits which brought to light the debilitating drug-induced side effect [p. 125] were the drugs' labels revised include a warning about TD or other severe side effects, until 1973 [p. 121] Furthermore, when patients were taken off these drugs, it was noted that they suffered, an acute "discontinuation syndrome" (i.e., "rebound psychosis" "behavioral toxicity") that was often more severe than the original symptoms of the illness.<sup>330</sup> These drugs' severe adverse side effects are symptoms of the drugs' disruptive effect on the neurotransmitter system and on brain function. Dr. Hyman's 1996 reports (discussed above) shed light on these drugs' profound impact on brain function, thus explaining why patients' functioning worsened over time on the drugs. As Hyman explained, the drugs destabilize normal brain function, rather than normalize a "chemical imbalance" as has been claimed.<sup>100</sup> [p.153]

Despite the irreversible damage, and despite the unfavorable comparison outcome measurement studies, such as data from the World Health Organization, demonstrating that the outcome of treatment with neuroleptics has worsened rather than improved patients' recovery<sup>331</sup> the drugs ("chemical restraints") continued to be promoted as brain chemistry "normalizers." Indeed, as Whitaker points out, they have been touted as "wonder drugs" and credited with facilitating deinstitutionalization -i.e., the emptying of state psychiatric hospitals and presumably saving taxpayers millions (if not billions) of dollars each year. A 1994 editorial by the Committee on Psychopathology of the Group for the Advancement of Psychiatry (GAP)<sup>332</sup>, in *Hospital and Community Psychiatry* points out, "psychiatry has a phobia about outcome studies...Such information threatens their practice and the concepts that support it." [p. 1165]

In recent years, researchers using imaging techniques began to report various abnormal changes in brain structure, volume, and neural sensitization--all caused by neuroleptic drugs.<sup>333</sup> For example, in 1994, Drs Chakos, Lieberman et al,<sup>334</sup> reported that brain scans of young schizophrenia patients exposed to neuroleptic drugs for 18 months had shown abnormal enlargement of the brain caudate after drug treatment. Yet, in a 1997 review, Dr. Lieberman and colleagues at Hillside Hospital<sup>335</sup> proposed "an exciting new strategy" to examine the pathophysiology of psychosis. Rather than evaluate the empirical evidence pointing to the effect of drug treatment, they hypothesized "susceptibility" in schizophrenia patients to develop "neurochemical sensitization" and a deteriorating course of illness. [p. 208] The authors describe the findings of a series of chemical provocation experiments-between 1968-1997-- in which psychostimulant drugs (e.g., methylphenidate, amphetamine) were used in schizophrenia patients and non-patients to induce psychosis for experimental purposes. [p. 214] In the 1990's the purpose of these experiments was to obtain "functional imaging scans (SPECT or PET)." [p. 214] The authors conceded, however, "these studies were of patients who had previously received antipsychotic drug treatment... consequently, the possibility that this was a treatment effects cannot be entirely ruled out." [p. 214] They also acknowledged that repeated exposure to stimulants had caused sensitization in animal models and non-schizophrenic, normal controls. [p. 209]

While acknowledging poor patient outcomes, Lieberman and his colleagues at Hillside Hospital, steadfastly refuse to examine the empirical evidence or even to consider the possibility that neural sensitization may not be caused by a genetic marker, but rather by "chronic administration of psychoactive drugs" which (Hyman and others suggest) "may alter the molecular constituents of neurons, thus, the functional activity of neural circuits in which the neurons exist, and ultimately the behavior of the organism subserved by these circuits."<sup>336</sup> The search for the elusive biological marker has yielded no evidence in forty years of any intrinsic brain differences between nor-

mal and schizophrenia patients.<sup>337</sup> The resistance within psychiatry against analyzing recovery rates and treatment outcomes<sup>332</sup> or comparing them to non-pharmacologic treatments (in the US and in other countries) would appear to be a consequence of the inordinate influence of the drug industry on psychiatry. Few in the profession are willing to question the value of psychotropic drug treatments or to evaluate whether the benefits for patients outweigh the risks.<sup>114,213,330,339</sup> Instead, atypical antipsychotics-such as olanzapine, risperidone, quetiapine, sertindole-are currently being promoted without reservation much as the standard neuroleptics had been. The atypicals, it is claimed, are "well tolerated...safe and effective... with few and infrequent side effects..." and the profession is lending support for broadening the market for the new (more expensive) drugs by speculating, "as therapeutic opportunities evolve and diversify, atypical antipsychotics, because of favorable adverse-effect profiles, will have enhanced patient tolerability and use in nonpsychiatric conditions."<sup>340</sup> A Harvard team recently reported "promising findings" to support combining both olanzapine and Prozac: "The combination of olanzapine and fluoxetine appears to be a promising, safe, and effective treatment."<sup>341</sup> That pronouncement surely met with enthusiasm at Eli Lilly headquarters since olanzapine (Zyprexa) is the company's blockbuster best selling drug and fluoxetine (Prozac), whose sales slipped will be well served by a recommendation for dual prescribing from Harvard researchers.

#### Case 13: Two Competing Approaches to "Schizophrenia Prevention:"

A "schizophrenia prevention" experiment currently being conducted at Yale University exposes healthy adolescents, some as young as 12 years of age, to the effects of a powerful neuroleptic drug, olanzapine (Zyprexa).<sup>342</sup> The difficulties involved in diagnosing schizophrenia are well known to clinicians and researchers. Dr. Barbara Cornblatt, director of the division of high-risk studies at Hillside Hospital, a major center for schizophrenia studies, has acknowledged that psychiatrists cannot accurately diagnose schizophrenia, much less predict who will get it: "Nobody yet knows what the early symptoms are. . . we don't even clearly know what the level of risk is; we don't know if 5 percent or 40 percent who are identified with suspected risk factors are going to become ill"<sup>343</sup> Indeed, a Harvard team of psychiatrists acknowledged in August 2002, the absence of any scientific diagnostic instruments: "there are no universal signs of schizophrenia, indicated interventions for this disorder have a somewhat broader definition than those used in other health fields where clearer signs are available (for example, borderline hypertension for heart disease."<sup>344</sup> The subjects are too young to be legally capable of giving valid, informed consent, or to appreciate the degree of risk to themselves, nor are they possess an understanding of the scientific uncertainty underlying the experiment.

Contrary to the alarming rhetoric by promoters of the "schizophrenia prevention" study, the incidence rate of



schizophrenia in siblings of diagnosed patients is estimated within the range of 2% and 9%.<sup>345,346</sup> Thus, at least 91% of siblings being recruited at Yale will never become ill with schizophrenia if left alone. That is not the message being conveyed by psychiatry either to parents or the public. Reports about the experiment in influential newspapers such as the *Wall Street Journal (WSJ)* and the *New York Times* carried headlines that betrayed a commercial pharmaceutical pitch: "New Weapons in the War Against Schizophrenia"<sup>347</sup> and "Doctors Try a Bold Move Against Schizophrenia."<sup>343</sup>

Surely, the investigators and the Yale institutional review board must have been aware of the existing body of published clinical evidence showing profound changes in the central nervous system with demonstrable physical and neurological impairments caused by long-term exposure to neuroleptics<sup>298,334,335</sup> As noted above, olanzapine, the antipsychotic drug used in the Yale experiment, is known to have produced serious adverse side effects in 22% of adult patients with schizophrenia in whom it was tested for a short period of time.<sup>349,318,299</sup> The death rate in pre-marketing clinical trials was higher than in any other neuroleptic drug trial.<sup>81</sup>

Given the fact that by any standard of the time 91% or more of adolescents recruited for the Yale experiment were not even "at risk" of the condition, there seems to be no justification whatever for exposing these adolescents to a drug linked to severe-sometimes irreversible, and occasionally fatal-effects. Even Dr. Rex Cowdry, a former NIMH researcher, expressed alarm about the "schizophrenia prevention" experiment on healthy adolescents. "No one knows the long-term dangers of putting such patients on antipsychotic drugs," he told the *NYT*.<sup>343</sup> Nevertheless, the FDA approved it and the NIMH (partially) funded the experiment. None of the subjects met the diagnostic criteria for schizophrenia, and few, if any, were likely to derive any demonstrable personal benefit from the experiment, a requirement under federal regulations. They were selected for the study because their siblings had been diagnosed with schizophrenia and the researchers had *hypothesized* that the adolescents may be "at risk" for schizophrenia. Their hypothesis lacks scientific validity-as did the "at risk" for violence experiment. In both cases, children were unjustifiably exposed to the risks of psychoactive drugs. In neither case was there a demonstrable condition; therefore, an invasive treatment is inappropriate. Yale and Harvard researchers recently acknowledged there are no objective tests or biological markers for schizophrenia.<sup>349,350</sup>

The basis for the researchers' conjecture-and for the olanzapine experiment-was the suspicion that because one sibling had schizophrenia, other siblings may, possibly develop the condition in the future. That suspicion, however, is not backed by any scientific evidence. Whereas evidence demonstrating the drug's propensity to cause iatrogenic pathology is not based on conjecture. Ninety one percent of the adolescents recruited for the Yale study will not get schizophrenia-which is not necessarily a

chronic, lifetime disease, as is diabetes. These youngsters incur a very significant risk of contacting diabetes with its multiple debilitating pathologies. Indeed, as a result of their participation in the Yale study, they may be shortening their life expectancy by 10 to 15 years if they contact diabetes. One must wonder what of this vital information was disclosed to the subjects and their families in the informed consent forms?

Within a year of the Yale study announcement, the *WSJ* reported: "Radical Study on Schizophrenia May Be Expanded" to a multinational study targeting 1,500 teenagers. The *WSJ* reported that pharmaceutical companies provided \$25 million dollars for the project. A Harvard team led by Dr. Ming T. Tsuang<sup>346 350</sup> has also embarked on the "schizophrenia prevention" bandwagon that (in their own words) "is a radical departure from tradition." It is a far-reaching strategy designed to reformulate the diagnosis of schizophrenia by abandoning the DSM IV diagnostic manual criteria,<sup>350</sup> and broadening the "treatable" patient base from diagnosed patient to healthy first-degree relatives. Tsuang and colleagues argue that psychosis, as the sine qua non of schizophrenia should be abandoned as a diagnostic criterion for schizophrenia. Instead, Tsuang leaves investigators great latitude by proposing the term "schizotaxia," which they acknowledge is "still an evolving concept" lacking diagnostic criteria.<sup>350</sup> (p. 1047) They claim that "schizotaxia" is either a precursor of schizophrenia or a "condition" without a psychotic component, characterized by neuropsychological deficits and negative symptoms that need to be validated. Lacking validation they nevertheless argue that "Schizotaxia" is a predisposition to schizophrenia that should be treated. Armed with this new rationale as justification, they cast a wider net to initiate pharmacological interventions for nonpsychotic first-degree relatives of patients diagnosed with schizophrenia. Their choice of drug is risperidone (Risperdal), Janssen's antipsychotic.

While the Harvard team acknowledge that the risk of schizophrenia for first-degree relatives of diagnosed patients is between 6% and 13%,<sup>344</sup> they claim that "schizotaxia" afflicts 20% to 50% of first-degree relatives. That bald assertion leaves little doubt about its psychopharmacological implications-families who are "hypothesized" to be "at risk" of an uncertain "condition" would greatly expand the "treatable" patient base. In August 2002, two articles and an editorial by Tsuang, et al, promoted "schizotaxia" and the "schizotaxia intervention protocol" for first-degree relatives of schizophrenia patients in the *Canadian Journal of Psychiatry*. However, Tsuang and his Harvard team were highly critical of Yale's primary prevention studies. Their criticism for exposing children and adolescents to toxic drugs is well taken:

"Prevention studies in children and adolescents have the unintended effect of labeling them as future schizophrenia patients. This raises the very real possibility of stigmatization and emotional harm to the subjects and to their families.

Moreover, the type of medications likely to be used in prevention trials may pose greater risks to children and adolescents than to adults. The use of antipsychotic medications to treat children, for example, has been limited in part because of concerns about side effects." Tsuang, et al further acknowledge that both considerations-stigmatization and drug-induced pathological side-effects-"preclude their use without solid evidence of their efficacy but even nonpharmacologic interventions can be psychologically harmful if their use is not predicated on a solid rationale."<sup>344</sup> [online p.3]

Both the Yale and Harvard experiments are being conducted without first demonstrating the predictive validity of the screening instruments; without evidence of the diagnostic validity of the condition; without evidence that a presumed "predisposition" will result in full-blown schizophrenia; without evidence that the drugs used to treat schizophrenia will prevent it; and without evidence of a favorable risk / benefit ratio to justify the risk of drug-related pathology.

The demonstrable risks of drug-induced iatrogenic pathology-including, acute weight gain, a ten-fold risk of diabetes, involuntary, disfiguring facial movements, not to mention akathisia, which is believed to be a catalyst for suicide-any one of these should have precluded the approval of such an experiment.

NIMH is already advancing the "schizophrenia prevention" strategy. Senior researchers who have launched a "deconstructing schizophrenia" initiative recently acknowledged in *Science*, perhaps for the first time, that after decades of research and a shift toward chemical treatment interventions the profession has failed to improve patients' lives. They acknowledge that drug interventions have produced "no real change in the outcome of the illness." They further acknowledge that: "A new generation of new drugs introduced in the early 1990s...don't normalize patients...In fact, [ ] *outcomes aren't much better now than in 1895, when the treatment was fresh air and water.*"<sup>355</sup> [p. 333] Among the researchers interviewed by *Science* is Dr. Carol Tamminga,<sup>353</sup> whose chemical provocation experiments at the University of Maryland were criticized for having induced psychotic symptoms (hallucinations) in patients by intravenously administering ketamine<sup>291,354</sup> to study its psychotic action. Those experiments evidently yielded little (if any) scientific information because Dr. Tamminga acknowledged in *Science* that schizophrenia is still "a disease whose mechanism is totally unknown." [p. 333] Dr. Patricia Goldman-Rakic of Yale debunks an oft-repeated claim when she acknowledged the absence of any distinguishing physiological difference in the brains of schizophrenia patients. Anatomical studies, she admits, are ambiguous, and there exist "no marked signature like plaques and tangles in Alzheimer's." [p. 333] And Dr. Wayne Fenton of NIMH acknowledged that the atypical drugs are not much of an improvement over the old: "The drugs we have today are based on elaborations

of drugs discovered serendipitously over 50 years ago." [p. 334]

These candid acknowledgements were made in the context of launching yet another major shift in schizophrenia research. This time "the keys to unlocking schizophrenia" will be sought not in the patients but in their first-degree relatives. Thus the search for effective treatments to alleviate the most confounding, disabling feature of schizophrenia-i.e., psychosis-is being cast aside. Instead, psychiatry shifts its focus of attention toward finding drugs to treat cognitive deficits, no doubt to be marketed as "intelligence boosters," an improvement for everyone.

### Conclusion and recommendations:

The direct beneficiaries of the experiments described in this paper were not the children who served as human subjects-indeed, none of the children benefited from these experiments. Most of the experiments described violated fundamental medical ethics principles-including the right not to be exposed to experimental risk without competent, voluntary, informed consent. The information sought could have been procured by other means, the risks were not justified, and most of the experiments lacked scientific rigor, thereby invalidating any findings. As noted, federal regulations prohibit the inclusion of children in research involving greater than minimal risk, when there is no potential direct benefit for them. Therefore, one wonders, what rationale led to their approval by IRBs since the risks to the subjects outweighed any anticipated benefits?

Undoubtedly, the primary beneficiaries of the experiments described in this paper were the pharmaceutical industry and its partners in academia-the investigators and institutions. Profit margins during this period have escalated at an extraordinary rate, higher than that of any other industry.<sup>355</sup> The pharmaceutical industry also enjoys greater government protections, subsidies, and tax incentives than any other industry, in part because its products are considered vital, and life-saving. More importantly, intense lobbying-more than one lobbyist for every congressman--generous campaign contributions, and a revolving door that encourages government officials to move into industry and vice versa, assure this industry unprecedented influence and government beneficence:<sup>356</sup> Public Citizen reported, "The federal government has conferred on the industry [17 years of] monopoly patents and patent extensions, tax credits worth billions of dollars a year, and research subsidies for both the most medically important drugs and also the top-selling ones."<sup>341</sup> Patent exclusivity protection applies even when the products do not offer any clinical advantage over existing products. Exclusive products are promoted with multi-million dollar marketing campaigns which former FDA Commissioner, Dr. David Kessler, described as "therapeutic-class wars": "for patients and providers it can mean misleading promotions, conflicts of interest, increased costs for health care, and ultimately, inappropriate prescribing."<sup>357</sup> Indirect beneficiaries of the experiments described in this paper include the professional associations and journals that had grown

dependent upon the financial support (or advertising income) from the pharmaceutical industry—just as academic centers have. Together these special interest groups comprise, what health care analyst Daniel Greenberg, calls, "Big Science": "They are the quintessential special interest group, and in effect, they make the oil industry look like a piker."<sup>31</sup>

In his last speech as President of the United States, in January, 1961, Dwight D. Eisenhower warned against the threat of the "military industrial complex:" "In holding scientific research and discovery in respect, as we should, we must be alert to the equal and possibly opposite danger that public policy itself could become the captive of a scientific-technological elite."<sup>358</sup> In his dissenting statement as a member of the ACHRE committee, Dr. Jay Katz<sup>359</sup> expressed concern about the inadequacy of the current regulatory scheme to ensure that the rights and interests of individual citizens are protected in the context of research. Current regulations do not lend themselves to grapple with essential conflict of interest issues. Dr. Katz asked, "When, if ever, should conflicts between advancing medical knowledge for our benefit and protecting the inviolability of citizen-subjects of research be resolved in favor of the former?" The documents examined by ACHRE revealed that government officials in concert with their medical advisers more often than not merely paid lip service to informed consent. "Whenever they considered it, they worried mostly about legal liability and embarrassment. They were not worried or embarrassed about their willingness to conscript unconsenting patient-subjects to serve as means in plutonium and whole body radiation experiments. All this is a frightening example of how thoughtlessly human beings, including physicians, can treat human beings for "noble" purposes."

This paper has argued that a conflict of moral values exists between the moral imperative to protect the rights and welfare of the individual—particularly vulnerable individuals such as children—and utilitarian pragmatism, which threatens to overturn the ethical parameters of permissible research involving children. Utilitarian business ethics serves the needs of the burgeoning academic medical research industrial complex. But utilitarianism collides with those humanist principles that are integral to medicine and its "do no harm" dictum. Research is always fraught with ethical dilemmas. Now more than ever there is the very great temptation to obtain research subjects who, from the perspective of research stakeholders, are an increasingly scarce commodity.<sup>360</sup> Children who are incapable of protecting their own best interests are being sought to fill that unmet need, and to accelerate the pace of marketing new drugs for use in the pediatric population. Critics who were cited in this paper are appalled by this industry's pervasive influence in recasting the very culture of medicine. Daniel Greenberg put it this way:

A relentless quest for money pervades science—and almost anything goes to acquire it, including commercial deals between universities, scientists, and

industry that trade away basic traditions of science: openness, collegiality, and protection of human subjects of research. In scientific journals and in conferences, conscience-stricken scientists despair over ethical erosion in their profession. Debates rage over codes of conduct to assure ethical behavior, but the lure of mammon remains a powerful force in the life of science.<sup>361</sup>

From the many examples here presented and from others that continue to surface,<sup>362</sup> it should be clear that the current system for the protection of human subjects of research is unsustainable. As the experiments presented demonstrate, the existing system fails to protect children in part because it depends for its oversight on local IRBs that operate under the influence of corporate and institutional interests and within a culture of little or no public accountability. In-house committees are often pressured by investigators and administrators to expedite research protocols. Committee members are caught between the institutions that employ them and the federal mandate that places responsibility on them to protect the subjects of experiments carried out by their institutions. Not all, but many committees fail, yet we do not know why some succeed. There has never been an assessment of why some IRBs function effectively while others don't. Doubts about (and interest in) the effectiveness of IRBs and government oversight agencies tend to follow in the wake of high profile scandals. Unless viable safeguards are established, the vulnerable are indeed in danger of becoming a "risk bearing" ("at risk") underclass.

There is an urgent need to re-examine, revise and reconstruct the current research protection system in the US, and to replace its inconsistent, often contradictory, guidelines with a rational, ethical framework capable of holding both researchers and institutions accountable. The current system needs to be transformed from a culture of secrecy to a community of transparency and accountability. The transformation, however, will require the enactment of national legislation and mandatory, independent checks and balances to protect the rights and welfare of human research subjects at least as vigorously as the Animal Welfare Act of 1966 protects the rights and welfare of laboratory animals.<sup>50</sup>

#### **Recommendations:**<sup>363</sup>

The enactment of a National Human Subject Protection Act that should, at the very least:

- ♦ Govern ALL human research, regardless of the source of funding.
- ♦ Establish a national electronic database for registering ALL research involving human subjects. The database should include research protocols, informed consent documents, and documentation of all serious adverse events related to experimentation and/or drug use. Such a database can facilitate evidence-based risks assess-

ment, disseminate knowledge in a timely fashion, and minimize duplication of human experiments involving risk.

- ♦ Convene an independent National Review Board at least 1/3 of whose members are not scientists or industry dependent. Such a makeup can go a long way to ensuring that the values of society at large are represented in the research endeavor.
- ♦ Comply with the Declaration of Helsinki principles, ensuring that in every study each human subject receives treatments that are at least as safe and effective as the best currently available treatment. Also, adopt the recently adopted Helsinki requirements to fully disclose all funding sources and to publish all research findings, including negative findings.
- ♦ Clearly identify whose responsibility it is for ensuring that research is conducted ethically, which or who is the reporting authority, and where exactly are the locations of the federal oversight and enforcement.
- ♦ Clearly specify the legal sanctions and penalties--both civil and criminal-- for violating the proposed law.
- ♦ Require a no-fault insurance for all individuals that participate in human subject research. This will help guarantee every human subject medical aftercare and compensation if harmed.

Additionally, it is clear to this author as it was clear to the Maryland Court of Appeals: "the scientific and medical communities cannot be permitted to assume sole authority to determine ultimately what is right and appropriate in respect to research projects involving young children."<sup>262</sup> Federal regulations are predicated on our moral responsibility to protect children-who are not competent volunteers-from being subjected to medical or behavioral experiments that are not in their best interest. However, there is no effective enforcement mechanism to ensure that these regulations are enforced. Evidence demonstrates that the research community often violates medical ethics for expediency. Therefore,

#### **10 recommendations for the protection of children:**

- (1) Inasmuch as drugs have unwanted side-effects, and medical research involves risks of harm, only children whose narrowly defined currently diagnosed medical conditions can potentially be helped, should be recruited to test drugs or other medical devices or procedures.
- (2) Legislation for the protection of children's health and welfare should put the burden of proof on those seeking to conduct research on minors under the age of eighteen to establish the existence of "compelling circumstances" that justify such research on children. Investigators must provide the criteria for

demonstrating that the benefits of the research outweigh severity, duration, frequency and likelihood of the risks. Children must be assured that current "best medical practice" standards of treatment will be compared to any new or experimental treatment, and that those consenting on their behalf can be held accountable for making research decisions that are in the child's best interest.

- (3) Children should not be recruited for experiments involving greater than minimal risk on the basis of vague speculations about them being "at risk" of some unproven condition that may or may not ever materialize. Before research involving children can be considered, a rigorous set of standards must be established so that the phrase "at risk" can be identified by specific demonstrable risk factors as currently existing on a more likely than not basis. Investigators must demonstrate that the nature, severity, duration, and frequency of the risk is greater than the intervention proposed.
- (4) All clinical trials involving the use of children, as previously defined, should provide no-fault insurance coverage for both short-term and long-term adverse effects that may arise from or in the course of participation in the stated clinical trials.<sup>364</sup>
- (5) The pool of child subjects must not constitute an unfair burden on disadvantaged families who may not have access to current "best practice" standards of treatment in their community. Thus, care must be taken to ensure that the population from which sick children shall be recruited represents families from diverse socio-economic strata. When children are sought from a specific ethnic or socio-economic population, evidence must be provided demonstrating approximate proportion to prevalence of the condition under study to that specific population (in the United States or elsewhere).<sup>365</sup>
- (6) The recruitment of children with financial enticements to their caregivers should be prohibited.
- (7) The record demonstrates that the current system of review of both the scientific and ethical components of research protocols involving sick children, have failed to protect children such as nine-month old Gage Stevens (Case 3) or eight year old Jennifer Munger (Case 3) from harmful experiments that killed them. Therefore, there is a need for oversight by a "Children Protection Committee" in addition to review by an institutional review board (IRB) that would serve as the child subjects' advocates, monitoring their selection, assessing the reasonableness of their parents' consent, the adequacy of disclosure in the informed consent documents, and monitor-

ing their continued willingness to participate in the research.<sup>366</sup>

- (8) The majority of the Children Protection Committee (51%) should be drawn from the community, among them representatives from the same socio-economic strata as the children in the specific clinical trial.
- (9) All of the members of the ethics review board and the Children Protection Committee should be vetted for complete absence of conflicts of interest.
- (10) The expenses for the process of safeguarding children's best interest in research-including community members who are involved in implementing the research review and monitoring process-should be paid from a government fund established for that purpose. The government should, in turn, be authorized to recapture its costs, including oversight of all pediatric research, by way of reimbursement from the drug or medical device manufacturers who are eventually licensed to market such drugs or medical devices that result from approved pediatric research.

Nothing less than a radical overhaul of the current system will protect children and vulnerable adults from harmful experimentation. In an era in which affordable health-care has slipped beyond the reach of many citizens and medicine has aligned itself with the pharmaceutical industry to produce marketable, although not necessarily improved, pharmaceutical products, the burden of risk borne by research subjects must be lowered and the ethical and legal responsibility borne by the research establishment must be raised.

Last, there is need for the involvement of other professions and the judiciary rather than sole reliance on an IRB system to oversee the conduct of biomedical research in the United States. Existing child welfare law, specifically the provisions of the Child Abuse Prevention And Treatment Act (CAPTA) OF 1996 (PL 104-235) requires that social workers, teachers, physicians, nurses, lawyers and other professionals report instances of suspected child abuse to the appointed state authorities for investigation and possible referral to children's courts for adjudication. The "good faith" reporting of suspected research abuse by anyone should also be encouraged as a prevention measure. ☺

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may be conducted "only if...the risk is justified by the anticipated benefit to the subjects" and "the anticipated benefit is at least as favorable to the subjects as that presented by available alternative approaches" (i.e., therapeutic justification). 45 CFR 46.406: "Research involving a minor increase over minimal risk and no prospect of direct benefit to the individual subjects" "only if the risk represents a minor increase over minimal risk" and the intervention or procedure "is likely to yield generalizable knowledge about the subject's disorder or conditions which is of vital importance for the understanding or amelioration of the subject's conditions." 45 CFR 46.407: "Research not otherwise approvable which presents opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children." Under those circumstances the Secretary, of the Department of Health and Human Services can approve the research after convening a panel of experts, and providing the public an opportunity to review and comment. [Emphasis added] These regulations were adopted to protect children from experiments that are contrary to their best interest, but left it to local boards to interpret and enforce the regulations.

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69 Personal communication. The claim was made during deliberations of the Children's Workgroup (a subcommittee) of the National Human Research Protections Advisory Commission (NHRPAC), of which the author was a member. The Workgroup's several recommendations were not based on any examination of cases that had failed to meet regulatory standards. They were formulated on the basis of subjective preferences. Of note the author's written dissenting opinions that had been submitted were never forwarded or even mentioned. Thus, the public record does not reflect the minority opinion and is, therefore, inaccurate. In the interest of greater transparency, the other members of the Children's Workgroup are listed: Alan R. Fleischman, M.D. (Chairperson), Senior Vice President, The New York Academy of Medicine; Jon Abramson, M.D. Dr. Grave Gillman, Chief, Endocrinology, Nutrition & Growth Branch National Institute of Child Health & Human Development, (National Institute of Health); Weston M. Kelsey Chair, Department of Pediatrics, Wake Forest University School of Medicine; Myron Genel, M.D., Associate Dean, Government & Community Affairs, Yale School of Medicine; Susan C. Kornetsky, M.P.H., C.I.P. Director, Clinical Research Compliance Department of Clinical Investigation, Children's Hospital, Boston; Felice J. Levine, Ph.D. Executive Officer, American Sociological Association; Mary Faith Marshall, Ph.D. Director of Program in Bioethics, University of Kansas Medical Center; Jonathan D. Moreno, Ph. D., Emily Davie and Joseph S. Kornfeld Professor of Biomedical Ethics Director, Center for Biomedical Ethics, University of Virginia Health System; Robert Murray, M.D., MS (Genetics), Chief, Division of Medical Genetics, Chairman, Patient's Rights and Organizational Ethics Committee, Howard University Hospital; Robert "Skip" Nelson, M.D. The Children's Hospital of Philadelphia, Department of Anesthesia and Critical Care Medicine; Mark A. Riddle, M.D., Johns Hopkins Medical Institutions Director, Division of Child & Adolescent Psychiatry; Rosemary Roberts, M.D. Deputy Director of Pediatric Drug Development and Program Initiatives, Center for Drug Evaluation and Research, Food and Drug Administration; Susan L. Weiner, Ph.D., The Children's Cause, Inc.

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icaltrials.gov/ct/gui/c/1r/show/NCT00001960?order=1&JServSessionIdznce\_c\_t=w18gjcjmj>.

74 See, Congressional statement by Stephen Spielberg of R.W. Johnson Pharmaceutical Research Institute: "The critical point, however, has been the expanded interest and commitment on the part of the pharmaceutical industry to pediatric drug development under FDAMA. There have been several meetings including representatives for the industry, FDA, the National Institute for Child Health and Development (NICHD), and the American Academy of Pediatrics which have addressed critical scientific, medical, and ethical issues to assure excellence in pediatric clinical trials." See note 19.

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102 U. S. Drug Enforcement Agency (DEA). 2000. Congressional testimony, Committee on Education and the Workforce: Subcommittee on Early Childhood, Youth and Families, May 16. DEA data shows that the U.S. produces and consumes 85% of the world's production or Ritalin, and that 80% of the prescriptions for either methylphenidate or for amphetamines are written for children diagnosed with ADHD. Further, the number of prescriptions written for ADHD has increased five fold since 1991. With such expansive use of drugs for childhood behavioral disorders, no one has yet explained why, for example, US use of Ritalin "differs significantly from medical practices in the rest of the world," or why Ritalin and amphetamine use differs considerably from state to state—and from community to community—within the US. Some communities have almost no apparent use for Ritalin, while others diagnose 10% to 20% of their student population as having ADHD. Even more perplexing is the fact that although 40% of all US prescriptions for Ritalin are written for children ages three to nine, the manufacturer's FDA-approved label indicates that Ritalin is not approved for use in children under the age of six.

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online at: <http://www.aafp.org/afp/20010901/817.html>

107 U.S. Subcommittee of the Committee on Government Operations, House, Hearing, 91st Cong., Sept 29, 1970, [p. 131 "What troubles me more now than before I started is the inexactitude of all these programs. There is no evidence that they are all hyperkinetic children and you say that everything is perfect? ... a 6 year old with a dosage up to 50 milligrams, are you telling me there is no dependency? Where [we know] it does create dependency? ... We are talking in broad context of hundreds of thousands of children. The thing that really troubles me in this is a certain glibness about the experimentation on young children in this country, used as guinea pigs... we talk about credibility gaps and generation gaps... I just wonder whether or not we are justified in proceeding in any direction until we have more certain knowledge of the total broad effect [of the drugs]." Cong. Cornelius Gallagher [p.29]

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109 See, Lambert, NM, and Hartsough, CS. 1998. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *Journal of Learning Disabilities* 31:533-44. See also, Hartsough, CS, and Lambert, NM. 1987. Pattern and progression of drug use among hyperactives and controls: a prospective short-term longitudinal study. *Journal of Child Psychology & Psychiatry*. 28:543-53. See also, Lambert, NM. 1998. Stimulant Treatment as a Risk Factor for Nicotine Use and Substance Abuse. NIMH Consensus Conference. <http://www.add.about.com/health/add/library/weekly/aa1119v.htm>.

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113 Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. NIH Consensus Statement. 1998 November 16-18. 16(2): 1-37. Accessed January 30, 2003 online at: [http://odp.od.nih.gov/consensus/cons/110/110\\_statement.htm](http://odp.od.nih.gov/consensus/cons/110/110_statement.htm). The panel noted the following risks for children using stimulant drugs in its Statement: "psychostimulants have abuse potential; psychostimulants, particularly of amphetamines, may cause central nervous system damage [in high doses], cardiovascular damage, and hypertension. In addition, high doses have been associated with compulsive behaviors and, in certain vulnerable individuals, movement disorders. There is a rare percentage of children and adults treated at high doses who have hallucinogenic responses. Drugs used for ADHD other than psychostimulants have their own adverse reactions: tricyclic antidepressants may induce cardiac arrhythmias, bupropion at high doses can cause seizures, and pemoline is associated with liver damage."

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116 See, Diller L.1998. *Running With Ritalin: A Physician Reflects on Children, society and Performance in a Pill*. Bantam Books, 1998.

117 Agency for Health Care Research & Quality. 1999. Treatment of attention-deficit/hyperactivity disorder: Summary, evidence Report / Technology assessment number 11. AHRQ Publication No. 00-E005. All quotations are from Findings section, pp.4-5. Accessed January 15, 2003 at: <http://www.ahrq.gov/clinic/adhdsum.htm>

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<http://www.oralchelation.net/data/Psychiatry/data18g.htm>. For further discussion of pressures to use Ritalin, see Eberstadt, M. 1999. Why Ritalin rules? Policy Review. *Heritage Foundation* April-May: online at [http://www.policyreview.com/apr99/eberstadt\\_print.html](http://www.policyreview.com/apr99/eberstadt_print.html); Janofsky, M. 1999. Behavioral drugs focus of debate in colorado schools. *NYT*. November 25. Online at: <http://www.nytimes.com/library/national/112599behavioraldrugsedu.html>; Defino, T. 2000. Parents, schools face off over Ritalin: Some parents say they're being pressured to medicate kids. *WebMD Medical News*. March 2: online at <http://www.cnn.com/2001/HEALTH/conditions/03/02/cardiac.arrest.ap/index.html>; and Karlin, R. 2000. Ritalin use splits parents, school. *Times Union* (NY) May 7: online at <http://www.breggin.com/schools>.

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127 Spencer T, Biederman J, Wilens T. 2000. Pharmacotherapy of attention deficit hyperactivity disorder. *Child & Adolescent Clinical Psychiatry North America*. 9:77-97. p. 77.

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135 MTA. 1999a, p. 1073.

136 Ibid. See, table 5, pp 10082-10083.

137 Ibid. The investigators acknowledge in a note that there was no

improvement or difference in math and spelling between the treatment groups. [p 1080-81]

138 The MTA investigators claimed the study proved that "combined treatment and medication management treatments were clinically and statistically superior to behavioral treatment and community care in reducing children's ADHD symptoms." But they went on to state that combined treatment "yielded no significantly greater benefits than medication management for core ADHD symptoms." See, MTA, 1999a, p.1078.

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Richwood Pharm (Adderral), Solvay Pharmaceuticals (Luvox), Glaxo, Eli Lilly, Alza, Shire Labs, Medeva, Cephalon, and Somerset. 2000. Columbia University/New York State Psychiatric Institute, NYSPI Sponsored Research, Research Foundation for Mental Hygiene, Inc. Psychiatric Institute Division

([http://www.nyspi.cpmc.columbia.edu/nyspi/rfmhgrnt/Rf\\_spon.htm](http://www.nyspi.cpmc.columbia.edu/nyspi/rfmhgrnt/Rf_spon.htm)) Since then, apparently, that information - at least in the detail formerly available - has been removed from the website of NYSPI. Breggin evidently had a similar experience with earlier information. See Breggin, 2000.

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- 259 Ramsey "To attempt to consent for a child to be made an experimental subject is to treat the child not as a child. It is to treat him as if he were an adult person who has consented to become a joint adventurer in the common cause of medical research.... Non-therapeutic, non-diagnostic experimentation involving human subjects must be based on true consent if it is to proceed as a human enterprise. No child or adult incompetent can choose to become a participant in medical undertakings, and no one else on earth should decide to subject these people to investigations having no relation to their own treatment. That is a canon of loyalty to them...When he is grown, the child may put away childish things and become a true volunteer...[no one else could] volunteer him for submission to unknown possible hazards for the sake of good to come." Quoted in Glantz, 1998, (note 66).
- 260 In 1991, the British Medical Research Council noted that while a respectable body of legal opinion gives parents authority to consent their children for procedures that involve minimal risk, parents are precluded from consenting "to any treatment or procedure that is against the interests of the child." Therefore, the Council concluded, "non-therapeutic research involving children must not involve greater than 'minimal' or 'negligible risk.'" See, Glantz, 1998.
- 261 T.D. v NYSOMH, 1995, 626 N.Y.S.2d 1015.
- 262 *Grimes v Kennedy Krieger Institute & Higgins v Kennedy Krieger Institute*. Maryland Court of Appeals. August 16, 2001; online at: <<http://www.courts.state.md.us/opinions/coa/2001/128a00.pdf>>.
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- 264 Appellee brief. 2000. Myron Higgins, et al v Kennedy Krieger Institute April 3, 2000.
- 265 Three recommendations are of particular interest: (1) eliminating the distinction between therapeutic and nontherapeutic research; See, NHRPAC. 2001. (September 4) Comment Letter to HHS on 45 CFR 46 Subpart B. Online at: <http://ohrp.osophs.dhhs.gov/nhrpac/documents/oct01c.pdf>. (2) adopting rule to permit waiver of parental consent for research: "we request that the FDA utilize an aggressive interpretation of the Food Drug and Cosmetic Act to enable mature adolescents to consent to involvement in certain types of important clinical studies without parental permission. See, NHRPAC. 2001. (August 13). Specific Comment on FDA's Decision to Adopt HHS 45 CFR 46 Subpart D. EXCLUDING §46.408 (c). <http://ohrp.osophs.dhhs.gov/nhrpac/documents/fda.pdf>. (3) redefining "minimal risk" and "disorder or condition" to permit greater use of children in non-therapeutic experiments involving greater than minimal risks: "Thus, for example, prematurity, infancy, adolescence, poverty, living in a compromised physical environment, institutionalization, or having a genetic predisposition to future illness are some of the disorders or conditions of children that can, under the appropriate circumstances, warrant permissible research that presents levels of risk that are a minor increase over minimal without the prospect of direct benefit." See, Final Report from NHRPAC. 2002. Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research <http://ohrp.osophs.dhhs.gov/nhrpac/documents/nhrpac16.pdf>. The author's dissenting opinions from NHRPAC: Against linguistic tinkering Jan. 28, 2001: <http://www.ahrp.org/ahrpspeaks/RegulatoryTerms.html> Against waiver of parental consent to research. July 25, 2001: <http://www.ahrp.org/children/NHRPACreFDA.html>; Against experimental medical interventions on the basis of speculation. May 14, 2002: <http://www.ahrp.org/children/NHRPACdissent051402.html>
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- 268 The Alliance for Human Research Protection. Amicus Curiae brief in opposition of motion to reconsider. *Grimes v. Kennedy Krieger Institute*. October 1, 2001. online at: <http://www.ahrp.org/children/AmicusKKI.html>
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324 See Brown, P. and Funk, SC. 1986. Tardive Dyskinesia: Barriers to the Professional Recognition of Iatrogenic Disease. *Journal of Health and Social Behavior*, 27: 116-132. They stated: "tardive dyskinesia (TD), once regarded by psychiatrists as a rare syndrome, is currently recognized as the second most pervasive side effect following sedation of antipsychotic drugs." (p. 116). They pointed to two major obstacles to the profession's recognition of TD: first, clinicians were not trained to detect the symptoms or they were convinced it was a symptom of the disorder, not the drugs. They also note that "there was considerable avoidance to recognizing TD" (p. 121) and they found researchers deliberately selected data and study methods that would minimize the results. (p. 119) See also, Hansen TE, et al. 1992. Under recognition of tardive dyskinesia and drug-induced parkinsonism by psychiatric residents. *General Hospital Psychiatry*, 14(5):340-4.

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331 Whitaker. 2001. See table 7.1 "Stay-Well Rates for Patients Treated Without Neuroleptics" from six separate studies, p. 185; See discussion about data from the World Health Organization showing better outcomes, with significantly higher recovery rates for patients in developing countries where only 15.9% are given antipsychotic drugs, compared to developed countries where 61% are on drugs. See, pp. 226-232. Whitaker cites a study comparing the length of hospitalization of 1,413 first-episode male schizophrenia patients admitted to California hospitals 1956-1957. The study found that those who were treated with neuroleptics "tend to have somewhat higher retention rates." See, Epstein, L. 1962. An approach to the effect of ataractic drugs on hospital release rates. *American Journal of Psychiatry*, 119:20-35.

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336 Hyman. 1996. p. 159. See also, Madsen, 1998.

337 See, Valenstein. 1998 and Kaiser. 1996. See also, Wirshing, WC. 1994. What is schizophrenia? Special Issue, the ethics of neurobiological research with human subjects. Edited by Sharav, VH and Weisburd, D. *Journal of the California Alliance for the Mentally Ill*, 5: 30. Dr. William Wirshing, Director of Movement Disorders Laboratory, West LA VA, professor of psychiatry, UCLA, stated: "After three decades of toil no one has found convincing evidence for any abnormality whatsoever within the dopamine system in the brains of patients with schizophrenia...the theory that linked neurotoxicity to antipsychotic activity, to receptor affinity was so tidy and compelling that it seduced an entire generation of psychopharmacologists." See also, Castellanos, et al. 1996. "...three prior CSF studies [sic] do not support consistent CSF HVA abnormalities in ADHD. This same situation obtains in schizophrenia studies, in which patients and normals do not vary significantly in net CSF or plasma levels of HVA." ( p. 132). See also D'Souza, et al. 1999.

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363 The National Bioethics Advisory Commission (NBAC) called for change in its final report, recommending uniform standards and a single set of regulations for the protection of all human subjects regardless of the funding source; a national registry of clinical trials; compensation for those harmed; ensuring the level of review corresponds to the level of risk; and the increase of community members on IRBs to one third. The report failed to provide specific instances of abuse. See, NBAC. *Report and Recommendations of the National Bioethics Advisory Commission. Ethical Policy Issues In Research Involving Human Participants*. August 2001. Online at: <http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf> A report by a panel convened by the Institute of Medicine, in October 2002, acknowledged a series of events in the late 1990s that occurred due to "a confluence of factors—a combination of stresses, weaknesses, vagaries, and lack of accountability—that has pushed the system to the point where change must occur. Without active change the public trust in the research enterprise will be eroded." The panel recommended uniform standards for all human research; a national registry; and a no-fault insurance for all research subjects. See, Institute of Medicine. *Responsible Research: A Systems Approach To Protecting Research Participants*. October 2002. Online at: [http://www.iom.edu/iom/iomhome.nsf/WFiles/ResponsibleResearchFINAL2/\\$file/ResponsibleResearchFINAL2.pdf](http://www.iom.edu/iom/iomhome.nsf/WFiles/ResponsibleResearchFINAL2/$file/ResponsibleResearchFINAL2.pdf)

364 This is the identical phrasing of the language of state and federal work-

ers' compensation laws that provide such no-fault insurance coverage to virtually all employees of U.S. businesses.

365 This requirement reflects the ethical principle articulated in the Belmont Report relating to justice; namely, equal sharing of the burden and benefit of research.

366 The recommendation for a Children Protection Committee had been proposed by the Department of Health Education and Welfare in 1973 but never adopted. See 28 Fed. Reg. 31, 738 (1973).