

## **A Conversation with Adil Shamoo, Bioethics Activist**

**By Norman M. Goldfarb**

Adil Shamoo received a Ph.D. in biophysics from City University in New York in 1970. While an Assistant Professor at Mt. Sinai School of Medicine, he conducted laboratory research at the National Institutes of Health. In 1979, he joined the faculty of University of Maryland as a professor and served as chairman of the biochemistry department for three years. For the past 20 years, he has been a leading bioethics theorist, researcher and proponent for human subject protection.

### **What are "ethics"?**

To do the right thing, that is how simply I look at it. To distinguish between what is wrong and what is right. Imagine ethical conduct as a big circle. There is a small circle in the middle; that's the laws and regulations. Society has decided that if you violate the law or regulations we are going to punish you. Outside the little circle and inside the big circle are society's ethical mores and traditions. We deal with scandals by making the little circle larger and larger. But if the small circle becomes as big as the large circle, society will cease to function. That's why we need to promulgate ethical behavior as voluntary rather than as regulatory.

### **When did you first get into ethics?**

Back in the mid-1980s, Senator Al Gore and Representative Ted Weiss held hearings on issues of research integrity and fraudulent practices in science. Weiss's report, "Research May be Hazardous to Your Health," was very strong and very well-documented. The scientific community's response was disappointing; it was non-scientific, just denials and attacks on Gore and Weiss. The right response, the scientific response, is to consider a problem, study it, constitute solutions, and then move forward. I thought that I'd get into it, solve it in three years – to be very honest, that's what I thought – and get back to bench science. Once I got involved in it, it was a much more demanding field than I had expected. And, at the time, there hadn't been much work on research integrity.

My first contribution, in 1987, was to publish a letter to the editor in Nature suggesting audits for research data.<sup>1</sup> Zoltan Annau and I coined the term "data audit for research." Unfortunately, the idea did not catch fire since nearly all academic researchers opposed it. At present, there is some internal use of it in industry. In 1988, I organized an international conference on research integrity as a springboard for a journal, "Accountability in Research," which I still edit today. The conference was held in College Park, Maryland. We had about one hundred people and 25 speakers.

### **When did your focus shift to human research?**

I have a son with Schizophrenia, so I got involved with the National Alliance for the Mentally Ill – NAMI. I was a member of their Science Review Committee. In 1991, there was the Greg Aller case at UCLA.<sup>2</sup> He was in a schizophrenia trial but was a very well-functioning individual; he had a 3.9 GPA at UCLA. The study washed him out of his medication, as was the standard procedure at the time, and he deteriorated to almost becoming suicidal. He

had to drop out of college. His father was on a campaign all across the country against this kind of research.

NAMI was naturally concerned about the case. They asked me to look into it and issue a report. It took me a year and half to study the issue. I wrote a 25-page report and sent it to ten or 15 leading bioethicists for their opinion. They did not know me from Adam at the time. All of them agreed with the conclusions of the report and some apologized for not speaking more forcefully in defense of the mentally ill in research. When NAMI read the report, they liked it, but they did not want to deal with it. NAMI gets around 50% of its budget from the pharmaceutical industry. I forced them to hold a workshop, at least, which I chaired at their annual meeting. In 1991, Diane Irving and I wrote a paper, called "Accountability in Research Using Persons With Mental Illness."<sup>3</sup> That was the very first paper published on the topic. I am not exaggerating, within three or four years we distributed over ten thousand copies. That was what got me into human subjects.

In 1994, I organized a big conference with 43 speakers – "Ethics in Neurobiological Research in Human Subjects."<sup>4</sup> The American College of Neuropsychopharmacology issued a boycott because they felt that the conference would hinder research with psychiatric patients, but we solved that problem and the conference went forward.<sup>5</sup>

There was a lot of controversy. For example, one of my papers was accepted by the Journal of Clinical Ethics; I have the page-proof of the article. The Journal stopped publication because of a threat of lawsuits from a group of psychiatric researchers cited in my paper. I published an account of the behind-the-scene story.<sup>6</sup> In 1996, I published the article anyway in "Cambridge Quarterly of Health Care Ethics."<sup>7</sup> The paper showed data on meta-analysis of the schizophrenia research from the late 1960's through 1990.

I was bucking the industry as well as a huge number of psychiatric researchers who were routinely doing wash-out and relapse studies. In 1997, I published another article called "A Review of Patient Outcomes in Pharmacological Studies from the Psychiatric Literature, 1966-1993."<sup>8</sup> The findings were startling. A majority of the studies were of severe schizophrenia. Most of them would remove the current medication suddenly, not tapering it off. If you taper off medication, the relapse rate is about 15%. If you just stop it, the relapse rate is 40-60%. All that wash-out was done with out-patients, not in-patients. After that paper, the studies changed. Nobody does it that way anymore.

The most interesting finding was that there was not even a single report of suicide throughout those 28 years in the U.S. studies. Not a single one. In the European studies, the suicide rate was about 1%. In the U.S., there was a 13% drop-out rate. In Europe, it was 12%, 1% less than in the U.S. It may be coincidence, but it's very suspicious.

### **What is your current research focus?**

We are working on the step-by-step process of making an ethical decision. It is a very complex problem. Philosophers and bioethicists don't want to systematize the decision-making process, but I come from science. Any systematic method will fall apart in certain cases, but it can work well in the overwhelming majority of cases. We have a flow chart. You don't need to follow it to make a good ethical decision, but if you follow our process a dozen times, it becomes natural without looking at the flow chart.

### **When clinical investigators have to make an ethical decision, where are the trouble spots?**

Good people, and I believe that the overwhelming majority of people are good and noble people, do okay. There is a very small percentage of people who are pathologically

unethical, and we can't do much to reform them. There is a much larger gray zone of sloppy work and disregard of the regulatory and ethical issues. As a society, you want to reduce that gray zone as much as possible. Of course, you'll never get it to zero. With ethical people, all they have to do is sit down and think about it on their own. In all likelihood, the overwhelming majority will make a good decision. The reason we systematize the process is for training and to provide a framework for thinking through the issues.

Clinical investigators are under great pressure to shortchange the ethics because of financial conflicts. That to me is the source of all evil. There are other conflicts of interest, but financial is number one because it is measurable, because it has an effect, and because we live in a capitalist country where money talks a lot. In academia, career is money. Of course, trying to win the Nobel Prize, trying to be recognized, these are all pressures, but financial is much easier to measure. That's why we concentrate on it. Let's solve the financial and then we'll do the other ones.

### **You've written about the need for accurate counting of clinical research subjects.**

It is important to know the number of human subjects in research for a multitude of reasons. We need to know the number of those willing to volunteer, to identify disease-specific shortages, and, most importantly, to report fully the adverse events. In 2001, I reported, for the first time, that the total number of human subjects in research using the available official figures for fiscal year 1997 for federally supported research was seven million.<sup>9</sup> A year later, Eve Slater, then Assistant Secretary of Health and Human Services, published that for fiscal year 1998 there were twelve million human subjects in research funded by the federal government.<sup>10</sup> If you add up all the industry, investigator-initiated, and privately supported research the number is easily 20 million. That includes drug, device, behavioral, surveys, everything defined by the Common Rule as human subject research. About half are surveys and minimal risk studies. All the rest, about ten million, are drug, device and other interventions.

At least three million of those human subjects are in unregulated intervention studies. Neither the OHRP nor the FDA has any jurisdiction. That is a huge gap. If a study is not financed by the government or intended for a marketing license, it is exempt from federal regulation.

For the past 12 years, we at Citizens for Responsible Care and Research (CIRCARE) (<http://www.circare.org>) have advocated a National Human Research Subject Act. In 2002, Maryland passed legislation that says all human research in Maryland, regardless of the source of funding, must comply with the federal regulations. It's a simple law. All animal research has been regulated by federal law since 1966. Why don't we give the same protection to people?

### **What other reforms do you advocate?**

Last year, we published a paper in the "American Journal of Bioethics," Shamoo and Resnik. The title is "Strategies to Minimize Risks and Exploitation in Phase One Trials on Healthy Subjects." We said there should be a national registry of clinical trial subjects so people cannot be in more than one clinical trial simultaneously. There should be a period of time that passes between clinical trials. The names don't have to be public; the clinical investigator could have access with the subject's permission.

Five to six percent of our population have serious mental illness. About 15% have less-severe psychiatric problems. There are 300,000 homeless people with mental illness. I suspect we don't do an adequate job screening "professional" volunteers for mental illness.

There is no mandatory training and education for clinical researchers. Isn't that shocking? One of the big things industry can do is to mandate education and training, say thirty or forty hours for clinical investigators, with a transition period of three to five years. In three to five years they will no longer accept any clinical investigator who does not have a certificate of training. Now, there is maybe one hour during the investigators' meeting; what can you learn in one hour?

There is no uniform universal reporting for adverse effects. There are seven places in the FDA rules that talk about reporting adverse effects. In the Common Rule, the terms "adverse effect" and "adverse event" do not appear. There are similar terms, but there is no uniformity; it drives people crazy. Everybody interprets the regulations differently. OHRP has published a draft guidance document, trying to unify it. But it is going to be guidance, not law.

You do not need to report deaths. Read the law. In the real world, people are trying to make a living. There is pressure, body language pressure and unwritten pressure, not to report adverse events. Especially when you don't get paid for it. Reporting an SAE is a big headache. There are many cases in the FDA docket where a death was hidden by saying it was unrelated. The subject may have had a car accident, but if the drug is brain-active he could have had the car accident because of the drug. There are sites that report those deaths as lost-to-followup. Do you think people who are barely breaking-even on clinical research are going to fight the system? It needs oversight and a monitoring agency to make sure adverse events are reported.

### **What would a better system look like?**

You make it mandatory as part of the physician's and investigator's duty to report adverse events (or at least serious adverse events) for patients who are in clinical trials, period, otherwise he would be debarred. You make it web-based to make life easy. You could compensate them, \$5 or \$10 a piece. You also can make it a "no-fault" reporting of adverse events in order to remove the fear of liability. You do random audits; you interview the patients if necessary. If the IRS never audited taxpayers, do you think the cheating would go up or down?

### **What are your thoughts on globalization of research?**

It is a natural outcome of modern life. Protection of human subjects, other than in the United States and the Western world, has huge defects; and in some countries it is practically non-existent. Why do you think that 60% of all of our clinical trials are done in Brazil or Russia or China or India? I don't think that's an accident. It could be a disaster in the making.

Many sites here are excellent and many sites abroad are excellent. But I think the percentage of bad ones outside the United States is much higher than here. And we already know there are problems here.

### **What advice would you give to a young bioethicist about becoming an activist, getting involved in controversy?**

For the young bioethicist, these are all individual, moral judgments. Which risk do you take for the good of society? I cannot give a general formula. They have to evaluate each choice by their moral compass.

It's very hard. It really is. I was an adult. I came from Iraq. My life was in danger many times, fighting the Baathist Regime. What they can do to me here is nothing compared to

what they could have done to me in Iraq. I knew I would have problems. My grants would suffer. I knew I would pay a price and I did pay a price. This is the very first time that I mention it. The story is not about me; it's about human protection.

### **What do you see for the future of human subject protection?**

I am an eternal optimist. There are a lot of noble people in the industry and they really want to do the right thing. But the financial pressure is so great that sometimes, we are human beings, we sometimes shortcut human subject protection.

Tom Hayden said the revolutionary ideas of the 1960s are the realities of the 1990s. The revolutionary ethics of when I started in the early 90s are the realities today. Do you see any more wash-out and relapse studies now? Very few. There is a progress.

### **References**

1. Shamoo, A.E. and Z. Annau (1987). "Ensuring Scientific Integrity", correspondence. *Nature* 327: 550, 1987.
2. Robert Aller and Gregory Aller (1997), Chapter 11, P. 155 in: Shamoo, A.E., (1997). Editor, "Ethics in Neurobiological Research with Human Subjects" pp. 1-335, Gordon and Breach Publishers OPA, Amsterdam, B.V., The Netherlands.
3. Shamoo, A.E. and Irving, D.N. (1993). "Accountability in Research Using Persons With Mental Illness", *Accountability in Research*, 3: 1-17.
4. Shamoo, A.E., (1997). Editor, "Ethics in Neurobiological Research with Human Subjects" pp. 1-335, Gordon and Breach Publishers OPA, Amsterdam, B.V., The Netherlands. See Introduction as well as Chapter 33, P. 329 by Jay Katz in ref. # 4.
5. Shamoo, A. E. (1997). "Attempts At Suppressing Data", *Professional Ethics Reports*, of the AAAS, Volume X, Number 1, p.3-6, including two rebuttals.
6. Shamoo, A.E. and Keay, T. (1996). "Ethical Concerns about Relapse Studies", *Cambridge Quarterly of Health Care Ethics*, 5: 373-386.
7. Shamoo, A.E., Irving, D.N., and Langenberg, P. (1997). "A Review of Patient Outcomes in Pharmacological Studies from the Psychiatric Literature, 1966-1993", *Science and Engineering Ethics*, 3: 395-406.
8. Shamoo, A.E. (2001), "Adverse Events Reporting – The Tip of an Iceberg", *Accountability in Research*, 8: 197-218.
9. Slater, E., "IRB Reform", *The New England Journal of Medicine* 2002; 346: 1402-1404.
10. Shamoo, A. E. and Resnik, D. B. (2006), "Strategies to Minimize Risks and Exploitation in Phase One Trials on Healthy Subjects", *American Journal of Bioethics*, 6(3): W1 – W13.

### **Interviewer**

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