

THE COSTS AND BENEFITS OF A WELL-INTENDED PARASITE: A WITNESS AND REPORTER ON THE IRB PHENOMENON

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INTRODUCTION

Parasite has always seemed to me an unfair pejorative. True, the vast horde of worms and protozoa that feed on their human hosts take their nourishment from human bodies, and are, as such, a breed of vile leeches, free-loaders and spongers. But however despised, however lowly and hidden their thievery, their prey remains alive while they feast—something lacking from even the heroism and honorable character of the hunter. In this they are delicate and discerning guests. One may even say they are thoughtful, considerate, and appreciative. Their presence may actually confer a benefit—immunity, perhaps. But whether they benefit their hosts or not, they must remain adaptable and clever, for the dullards of the lot are soon destroyed.

I would be ungracious, and ill-advised as a writer, to draw heavy-handed analogies. The parasite idea is background, a kind of floating metaphor. The Institutional Review Board (“IRB”) movement did not find its way into human research as a living thing and make its home. It was introduced via federal funding as a measure of prevention against willful vile-ness—vileness such as occurred when the Nazi Party opened a rift in German culture and let through long hidden stores of mindless and perverse hatred, or when doctors in our own country willfully left patients untreated. The IRB movement was a measure of prevention against the unintended violence—in the form of injury to patients and normal control subjects—that new treatments can unleash. The IRB was intended to grow and live inside research, draw energy from researchers, and use the time and work of researchers to save their subjects from harm.

Time and work to save subjects from harm is, in fact, a simple equation: a balance of work and saving. Here is the center of the IRB controversy. How much work? How much saving? And, more importantly, saving from what?

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It must be evident already that I intend to offer a diatribe, unbridled animosity—that I intend an old-fashioned broadside such as has been thrown against—in ages past—a smug and oppressive ruling class that feeds off those it can control. This intention frees me from the ordinary restraints of scholarship; there will be no references, no demure balancing of assertion with its counterpoint. I also have my freedom because I do not pretend to hold credentials concerning government regulations, university governance, or the history of the IRB. Nor would I want any. I am a clinical researcher, with a long experience in research and in patient care. I have lived all my professional life among researchers, so I know what is said and I know what it is to live under the IRB hegemony.

For the past seven years, I have been principal investigator of our K30 Clinical Research Training Program. In that position, I teach young faculty how to plan and write their research plans and overcome their IRB difficulties—difficulties that are legion, demanding of time, and that often impose insuperable barriers to research. Apart from the K30 program, I have personally trained 91 physicians or Ph.D. scientists, have mentored an additional three (who are now prominent scientists), and presently mentor a group of seven physician scientists in nephrology. All have their IRB stories and scars. My knowledge of IRBs is grainy and particular, lacking the broad sweep of an expert assessment. Nonetheless, I bear witness as would a spectator to the king's court, and what I have to say is simple: The IRB movement began with a noble purpose but has degenerated into a tyranny that must be overthrown.

The IRB movement has enlarged its role such that it now usurps the authority that researchers should have and insinuates itself into the decisions that researchers should make. It is the worst of usurpations because it is a taking of power without responsibility. Researchers are the ones who must create science; they are the ones who must win National Institutes of Health (“NIH”) money and the approval of their peers; they are the ones who must recruit subjects and carry out the difficulties of science in real life; and they are the ones who ultimately bear responsibility for what goes wrong.

The IRB is a tedious, time-wasting, work-wasting machine that performs none of these functions. It merely weighs researchers down and benefits a small clutch of people at the researcher's expense. Worst of all, that small clutch of people is none other than a cabal of fellow researchers, who have set themselves up as judge, jury, warden, and—sometimes—executioner, capable of stopping research altogether.

What I offer for your consideration, dear reader, is a small group of actual protocols of my own making reviewed by the IRB at my institution, and by an outside IRB. They illustrate the problem. If the examples of IRB review seem absurd, even ridiculous, then you have understood them. Above all, they are true. Unbelievable, perhaps, but true.

I. PROTOCOL 8819: IN DEFENSE OF UNWANTED URINE

Urine, it is true, makes quite a difference in life. Have none and you will witness a catastrophe: dialysis and, in some cases, transplantation. Most of us make it, and in this homely manner keep our interiors fresh and well. But however valuable in the biological sense, once passed, urine plays a very small role in most people's lives—usually none.

But urine contains unusual molecules that laboratories like mine purify and study. These molecules prevent crystals from forming—ensuring, thereby, that most of us escape kidney stones. Thus, scrap urine—urine that has served its purpose in the human body—is ideal for testing assays for crystallization, assays we need for our research. Our kidney-stone patients provide samples of urine over 24-hour periods so we can analyze their stone risk factors and treat them. After our measurements are done, we have left-over urine waiting on sink-tops to be poured down the drain. It is this stuff—urine waiting to be unceremoniously discarded—that we sometimes harvest for its molecules or use for testing assays.

What are the risks to patients when we use their scrap urine? What do we save them from if we pour it down the drain? The protocol began in 1987 as Number 5369. Subjects were people who formed kidney stones. None of the subjects are identified by name, social security number, or other unique characteristic; results are merely coded by sex as either “stone formers” or “normals.” The protocol was approved in an expedited manner, with waiver of consent, and (as best one can tell reading the yellowing pages of my files) nothing more was required until 1997, when I submitted an entirely new application for the same work. This became protocol Number 8819 and it called for a total of 100 samples.

The procedural hurdles added for IRB approval in 1997 did not augur well for the changes imposed over the next several years. In 1998 and 1999, we were told to fill out a two-page request for re-approval, which was granted summarily. In 1999, the requirements became more involved and we also had to submit an amendment to add an additional investigator who would isolate proteins. This was also granted. In 2000 and 2001, we applied for and were granted requests for another year of approval. In 2002, in addition to another application, we were asked to submit a bibliography and summary of recent literature on the subject of urine proteins, presumably to shore up the benefits of our work in relation to the risks it posed. This was done—considerably increasing the time expended on the application process—and we were approved for another year. In 2003, we submitted another bibliography. In 2004, the bibliography had to also include the search engine criteria, which we duly added.

However, in 2005, troubles and irregularities began to crop up. It seems that we used far more than our original 100 urine samples specified in 1997 and could not account for all of them. How many in 2002? 2003? Since this is scrap urine, it is hard to be sure; a sample may show up in sev-

eral notebooks because it is merely a substrate for extraction of molecules. We went back to our notebooks and tried to count them up. This took real time—hours and hours. Ultimately, we came to about 375 scrap urines in 2002, 85 in 2003, and 50 in 2004.

In addition, there were questions about how the grant from the NIH that funded the research might relate to this protocol. We could not understand why our grant would matter to an IRB. Ultimately we were able to convince them it did not relate. The year 2005 was an expensive one for a renewal.

In 2006, the IRB ran into heavy issues with our use of scrap urine. They performed a review of all of our past submissions and found worrisome irregularities. Questions soon followed. Why does our research pose no more than minimal risk to subjects? Why will a waiver of consent not adversely affect the rights and welfare of subjects? Why is it impractical to do the research without a waiver? Will pertinent information be provided to subjects, if appropriate, at a later date? Then there was the vexatious matter of how many urines. We needed to submit an amendment to increase the numbers—we really have used too many. Finally, the grants became relevant. On reading our program project grant—over 1,000 pages in all—it appeared that some grant work might have used these scrap urines. If so, the IRB needs a copy of the grant for its files.

We have submitted the usual continuation application, with its bibliography, search criteria and summary of changes to the risk–benefit ratio. Yes, we have prepared an amendment to use more urine. And we have submitted a supplemental form W waiver of consent-authorization in the hope that we would not need to get the consent of all of the patients—a Herculean effort that would require consent from every single patient treated, because we do not know in advance the days when we will need urine.

We are now waiting for a response. It is a suspenseful time. Will we be permitted to use the scraps of urine? Or, to save our patients from harm, need we pour it down the drain? Furthermore, given the increasing interference of the IRB over the years, what will 2007 bring? Can we afford this protocol? Is the benefit to our research worth the cost in IRB overhead?

Here, in this homey protocol, we have some of the gist, the realpolitik of the IRB movement. Surely it is a jest to mention risk in the context of our protocol. Surely it is nearly insane to require any procedure at all to perform research using what is destined for the nearest toilet, what is unidentified and without value to those who produced it. Fools do not run the IRB, yet they require what no reasonable person would think necessary. No patient is protected from any risk because there is no risk in the first place. Regardless, some researchers are put to work running a fool's errand. The IRB is benign but costly, like a tapeworm: a slow draining of time and energy for another's purposes. Who benefits? Who, indeed?

II. PROTOCOL 11943: MY PAST AS A HOSTAGE

Beginning in October 1969, I began seeing patients with kidney stones who wanted medical treatment to prevent their recurrence. I saw every patient myself and, since 1969, have kept the information related to treatment in one or another of the many computers that have accompanied me; even today I have “machine readable” information from the first patient I saw. Because stone prevention requires that doctors know what causes the stones, I also made measurements in blood and 24-hour urine collections for all the patients in a laboratory I created for the purpose. By now, there are over 4,500 patients and over 30,000 laboratory studies, not to mention records for the thousands of x-rays that I have read and medications I have prescribed, whether taken or not. Most importantly, I have documented what ultimately happened to these patients: did the kidney stones recur, and, if not, what treatment was successful?

This collection is a treasure and one I have shared with the world in hundreds of research papers, book chapters, and reviews. This happy situation continued until 2002. In that year, what I had been doing for 33 years suddenly became the object of intense scrutiny. It seems in presenting the past I was compromising the privacy of the patients and possibly violating HIPAA.

How, I asked, are the patients placed at risk? Each one is a dot on a graph—a very small dot at that because there are so many. No patient was ever identified by name, address, or age. The research results are all averages. No patient’s story was ever identified by his or her unique case history. The research results are all summaries of groups. No one “out there” is interested in reading about “a case.” They want more heft. They want the whole massive undertaking summarized. They want statistics.

After I had compiled the patient data into summary form, I memorized the eighteen personal health identifiers from the HIPAA regulations. None of these, I told people in charge, is present in the papers or the books. The individual is nothing at all, detached utterly from life, a mere dot on a graph. The only people who see personal health identifiers are the individuals who make up the analysis tables, and those people are the researchers; we are the people who take care of the patients in the first place.

No matter. We duly produced an IRB document requesting to write papers from our past data. In response, we received a “Pending Conditional” status, meaning more information was needed. In this case, however, I am somewhat fortunate. I did not shred my emails, and have one from November 8, 2002, nicely stating what—had I said the same in my own words—would have sounded purely spiteful, willfully misleading, hyperbolic, or even insane. By luck, I can quote what would otherwise seem ridiculous:

Essentially, the only stipulation the Committee requested was that oral consent be obtained from all future patients to have their data used in your publica-

tions. They felt that this was necessary to be in compliance with HIPAA regulations and would be possible since all subjects are technically considered your patients.¹

It goes on to stipulate that oral consent obtained by reading an oral script to each patient was sufficient. No documentation is required, merely their unrecorded verbal consent.

Then comes the part I ponder most:

As your study does not use identifiers and has no risk the script should be very simple. This oral script will need to be voted upon at another fully convened IRB meeting.²

But wait, the study does not use identifiers and has no risk. So, the privacy of patients is uncompromised, and their safety is therefore not an issue. Why, then, IRB intervention?

The writer, a friendly and helpful person, goes on, in the same email correspondence:

As the discussion for your protocol was quite lengthy at the last meeting (Committee A), I strongly suggest sending the oral script to the next committee A meeting, December 2, 2002. It is my personal opinion that if you sent it to one of the other meetings (Committee B or C) new stipulations may arise.³

Really? Am I endangered?

New people—in this case Committees B and C—may not be as accommodating as Committee A. You know, good cop, bad cop; your friends versus the others. And, all the while, nothing is at stake, not privacy, not harm, not the slightest matter at all. Except one: my right to go on publishing the data. That is at stake.

On the one side of the balance, my right to publish. On the other, nothing at all; mere air. Less, than air, in fact, for air is at least something. The counterbalance contains mere vacuum: nothingness perfected in itself. Despite the revived interest by the IRB, nothing new is at stake except whether I can continue to publish old data. Eventually, we wrote a script and won approval. Months had gone by from the beginning to the end—months during which I was not permitted to analyze my own data. Subsequently, each year, we have filled out tables listing how many patients have entered the program, the total number of all measurements in blood and urine in our data banks, the papers we have published. Finally, there is the inevitable Pub Med search that seeks new publications that might affect our analysis of the risks imposed upon our unidentified patients.

¹ Email from an institutional review board administrator, University of Chicago, to Fredric L. Coe, Professor of Medicine and Physiology, University of Chicago (Nov. 8, 2002, 15:49 CST) (on file with author).

² *Id.*

³ *Id.*

III. HIPAA AND ME AND THE IRB

This unappealing Clinton legacy has the force of law. Medical researchers must comply with HIPAA or face the consequences. That I should face legal sanction for failing to comply with the law is not surprising. However, the IRB's involvement is not necessarily intuitive. The IRB does not review my proposed tax returns, despite the liability I would face for failing to pay my income tax. Why does the IRB review my proposed actions under HIPAA when the potential liability for noncompliance comes out of my pocket?

It is strange that I can be trusted to treat patients but cannot be trusted to publish from their old records unless I read to each patient an oral script asking permission to use their information at some future time. In my use of patient data, no personal identifiers are disclosed, and, therefore, there exists no risk that privacy will be violated. Nonetheless, an oral script is necessary, and I must read it to each patient before gathering their clinical information. Where is the regulation that requires I recite a script to my patients? My patients think I am daft when I do it. I say—it is HIPAA, it is the IRB. Most of my patients, when confronted with the script, say, what is HIPAA? What, indeed, is the IRB? My world, I tell them. My portion of paradise.

IV. ARE THESE MY ONLY PROTOCOLS?

I have another six protocols: five are reviewed by a commercial IRB, the Western IRB, and one is reviewed by my university's IRB. They all have offered me roughly similar experiences. Because my research (perhaps out of lack of nerve, ambition, or imagination) involves essentially no risks at all, or risks of so slight a character as to be unimportant, I have been freshly surprised, each time, that IRB requirements are as involved and elaborate as they are. One might have suspected the prior experiences were, perhaps, isolated aberrations, but with mounting experience, they are all simply examples of a general pattern: little or no risk, accompanied by massive IRB requirements serving an unclear purpose.

The protocol at my university involves measuring minerals in blood and urine during the course of a three-meal day in our clinical research center. The food is either made in our kitchens or bought in grocery stores. The only risks posed by the protocol are blood drawing, and infusing a marker substance for kidney function intravenously at 1/10 the dose used for a kidney x-ray. My researchers and I understand the need for review based on the minimal risk of an allergic reaction to the marker. Why must the tiniest change in protocol require a full packet of forms? Is so much bureaucracy warranted for a simple change to the timing of meals or blood drawing? Does a decision to put up signs to recruit normal subjects somehow impose a heightened risk of an allergic reaction? The latter change re-

quired not only submitting the request, but clearing the text on the signs, and even having each sign stamped with an official stamp.

All of this administrative work takes time. Our measured estimate for each variation is about one month. Why is it understandable that the microscopic risk imposed by the 1/10th dose of marker requires an IRB? Who says that a group of my peers is somehow better able than I am to assess the “risk versus benefit”? In fact, I am not the only doctor to review the risks. The NIH study section that funded the work had to decide if it was good enough to pay for. Where did the idea come from that any risk at all, any element howsoever slight, minute, and atomic in scale needs oversight? Every day, we cross the street or we drive cars. No one has succeeded in eliminating risk.

My other protocols with the Western IRB are worse—and considerably more expensive. For example, one protocol concerns the use of a large database to publish retrospective analyses of blood and urine measurements from patients who form kidney stones. This use of data has incurred remarkable IRB overhead, presumably so that the IRB can protect us from violating HIPAA.

Here, after two months of deliberation by the IRB and a \$500 fee, we finally received approval to use the analyses. Nonetheless, this exaction—a sizeable one to be sure—bought appallingly little research per dollar. Even though the same data is involved, we must submit each new retrospective analysis separately. There is no bulk discount, however. Each time we submit an analysis, the price remains the same: a \$500 fee and a two-month wait for approval. This amounts to \$500 and two months of delay to publish each scientific paper in a peer-reviewed journal.

The other protocols impose similar delays. In those other four protocols, we obtain 24-hour urine samples from patients cared for in practices around the United States—just urine samples, without any identifier except age and sex. Nonetheless, each local practice needs its IRB to sign off; months of waiting can go by. Our Western IRB, naturally, also takes its time—months—and our money. The delays mount up; months and months are lost out of every grant. It is not lethal, but it drains a lot from research, slowly.

V. WHAT DO WE SAY IN THE GULAG?

By “we” I mean, of course, the “we” who live here, who encounter each day the oppressiveness of the IRB consuming our time and work in its humdrum mode: eliminating non-existent risks imposed by old urine only after a lengthy deliberation about nothing. We also learn what it is to despise what we must satisfy, and despise even the people who do the work, though they are not themselves despicable but are merely doing what they are required to do. We learn that a laudable desire to protect patients from risk has become ridiculous in practice, because only the rare heroic research

poses enough substantive risk to make the practice necessary: gene treatments, new drugs, and, perhaps, odd diagnostic or surgical innovations. The risk in these types of research is obvious. Equally obvious, however, is that leftover urine and decades of old data impose no risk that justifies the costs imposed by IRBs.

When a noble desire gives rise to mindlessness—a costly mindlessness resulting in delays in research, yearly accountings and bibliographies, perpetual minor demands for forms and answers to questions that should not be asked—what can one think but that nobility has given way to a fool’s errand, fools demanding what only fools would request.

There is also the opaque oppression. The IRB process is secret and threatening. Decisions made by the IRB can be appealed only to the IRB that made the decisions. The university for which I work has no transparent appeal system. It is too costly to move against the grain. Not only is one’s time used up in doing the work, but grants from the NIH—the sole reason any of us are willing to accept the IRB requirements—are time limited. They run on average less than five years, a mere sixty months. A delay of two months is costly; any more delay can be destructive.

Most of all, one fears retribution, secret retribution meted out and veiled in procedural details. One might imagine a better way to do research, one that could avoid the IRB, but we cannot. One can adapt the research to appease the IRB, but often this makes the final product less valuable. One can contest the IRB’s action, sometimes effectively, sometimes not. Above all, one can wait. However, waiting is not costless if one has NIH grants, as their funds are time limited; budgets are by the year, and time can run out.

We have a patois. We talk about “getting an IRB through,” and look for a junior flunky to do the forms. We hope that, being nubile and pleasing, the person can get the approval letter. The yearly bibliographies are mocked.

Similarly ignored are the so-called consent forms, meticulously parsed by the IRB but, for the most part, unread by patients. I have tried reading them to patients and they demur: “Doc, let’s get by all the words,” they say; “I trust you, not that stuff on the paper.” It is not that they see us as the quintessence of moral virtue; it is that they see paper as just that, paper, whereas we are at least alive and accountable.

Ultimately, we who live in the IRB Gulag openly despise the IRB process, however much we are passionate advocates for the safety of research subjects. It is that we truly believe, and sense in our very beings, that the fluff and posturing of the IRBs make no difference. We can always deceive them, or evade them, and they know it.

What will or will not keep patients safe are the people actually doing—not reviewing—the work. That is why deaths and injuries keep happening

despite IRBs. Unfortunately, each incident seems only to further the justification for perpetuating the IRB.

VI. WHAT ABOUT MY FLOATING METAPHOR?

Like a revolver in the opening act of a play, no metaphor should be left unused. I suggest that a metaphor reveals a core of deeper reality. Some people benefit greatly from the IRB movement. They achieve status in their universities. They may be paid, or given freedom from other chores they enjoy less. Others like power. Some IRB programs are for profit. The IRBs are in the system of science, draw most of their sustenance from the efforts of those who must submit to them, and pass on that sustenance to some who control or—better said—are part of the IRB. They are what I proposed at the beginning: parasites that are better leached out sooner rather than later.

VII. ARE MOST PEOPLE IN THE IRB BAD PEOPLE?

Of course not. The people in our IRB are helpful, sympathetic, and rather aware—though in a veiled way—of the absurdities that abound in the process. None have displayed malice. I already quoted one who was more than helpful—truly my ally. I have read books about this disconnect between the immorality of actions and the essential morality of the actors; in history it is always about those doing what they are told to do, or paid to do, or ordered to do. The faculty members who review protocols are, of course, or fellow professionals who rotate such responsibilities. The bearer of the news is seldom the one responsible; one cannot blame anyone presently in view. Only “they”—those distant authors of the rules—are responsible. People whom I never meet and will likely never meet. Perhaps I would like them, too, if given the chance. Maybe, as we chatted over a dinner, I would understand their dilemma: even one injured patient in a whole institution brings on national wrath, so every research encounter is scrutinized, as if each were an equal risk. But they are not equal risks.

VIII. WHY IS THERE NOT MORE OUTCRY, MORE CONFRONTATION?

Perhaps the main reason is the false supposition that IRBs accomplish their stated objectives. Most, if not all, researchers, desire the safety of their subjects and believe the IRB ensures that safety. My protocols, they might say, are at the extreme low-end of risk, and therefore misrepresent the IRB process as deformed and ludicrous. Of course it could be argued that taken to its extreme the IRB process is indeed worthless, but that to surrender even one atom of prevention invites chaos.

When researchers serve on the IRB and share its safety concerns, no atom of prevention seems excessive. It is a vicious process, because no one can set a limit on the level of scrutiny required. Who will protect the patients from us, from physicians who do research? New drugs pose risks.

People die from gene experiments. It is as though the medical profession does not trust itself as being fully moral, and must elect some of its members to supervise the rest lest they commit evil, whether by intent, lack of care, ignorance, or error.

The IRB process did not save those who have died during drug tests or gene therapy experiments, and is not likely to do so in the future, because each time the unfortunate result was unforeseen, by the scientists and by the IRB. Researchers are not so lacking virtue and wit as to need supervision by—after all—peers. Who is to say that scientists on an IRB are better judges of proposed research than the scientists that funded the research with public money? Where is the evidence that requiring research scientists to write and print yearly Pub Med searches will protect subjects? Where is any evidence that informed consent documents inform subjects or save them from harm?

Perhaps, in the final analysis, we should demand that the IRB movement put itself to the effort of proving its own worth in the kind of trial we require of almost all other research innovations. Given the high cost of IRBs, they ought to be required to prove their utility, like any other new remedy. If a remedy is unproved, as is this one, the validity of the cure is in equipoise. We should execute a randomized, double-blind controlled experiment to tote up the final costs of IRBs and come to a rational decision to keep the IRB process or cut it away and be done with it.

