

Commentary

What is not found in the spreadsheets

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These facts are known: two children, subjects in the Kennedy–Krieger study of low-cost lead removal interventions, developed elevated blood lead levels. Their parents sued the institution, claiming that data had been withheld from them, and that this put their children in peril. The appeals court overturned a summary judgment issued in favor of the defendants, and indicted the KKI investigators, analogizing their behavior to those physicians who participated in the notorious Tuskegee syphilis study.

Without specific knowledge of what the study's informed consent letter stipulated, of when the blood and dust lead levels were known to the investigators and of how much time passed before the information was given to the parents, one cannot hope to draw an informed or fair conclusion about whether the investigators in the Baltimore lead intervention study committed an ethical or technical solocism. These are questions to be asked and answered in the trial, and any decision in the absence of these data is pure speculation. In the meantime, the sapient course is to heed Wittgenstein's injunction: "Whereof one cannot speak, thereof one should be silent."

Two questions arise: How can the painful experience of the Kennedy Krieger Institute research team inform us about the psychoethical milieu that surrounds clinical trials in general? And why did it become necessary or desirable to conduct studies looking for the least expensive means of removing lead from houses? By examining these two questions, we, who are involved in clinical investigations, could deepen our understanding of our craft and nourish our vestigial sense of humility.

1. Missing persons

Physicians have been given wide license to ask questions and perform acts that in other contexts would earn a lay

person at the least a punch in the nose. Not too many years ago, this license was regularly exploited, and trusting patients were frequently subjected to nostrums or procedures of uncertain efficacy and unknown risk. The tariff for admission to a charity hospital bed often was enlistment as an unknowing experimental subject in a clinical investigation. Informed consent is a relatively recent addition to the protocols of clinical studies.

Things have changed. Now, investigators must include, early in the design of any clinical trial, an application to the IRB for permission to perform the study proposed. They must also provide and read to the prospective subject a letter that supplies in considerable detail a description of the procedures, and a statement of their risks and benefits. IRB applications have grown in complexity and specificity that begins to rival that of the primary application.

As studies grew in size and complexity, the need for external auditing and *a priori* stopping rules became apparent. External Data and Safety Monitoring Committees, who decide when a level of risk demands a change in the protocol are now common. Many protocols specify stopping rules to be automatically invoked when a drug or procedure has been found to be either clearly superior or clearly dangerous. Letters of informed consent are now required to state, in considerable detail, what will be done to the subject and what are the attendant risks. These requirements are a frequent source of irritation to principal investigators. We resent the growing intrusion of barriers between us and the subjects of our inquiry, or of digressions between us and the answers we seek.

The overarching goal of clinical investigations is improvement of the human condition. If this is true in the abstract, why then does the study sample require the protection of a set of rules? Not because investigators are callous or evil, but because clinical studies by their nature do not grant subjects full status as persons. Epidemiology searches for normative content in *samples*, and deals with the differences in *people* by the use of summary variables such as standard deviations or confidence limits. There is

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simply no room in spreadsheets for the “I–Thou” relationship that Martin Buber described [2]. It is in the spreadsheets, not in the people, that the principal investigator finds the information he seeks, and in them, the “Thou” of an individual is replaced by “It.”

As a study is designed, the proposal written, the administrative structure to conduct it shaped and recruiting done, the patient as individual becomes more distant. As deadlines approach, problems appear and are dealt with, and subjects’ singular identities fade. An epidemiological study looking for a small effect could require as many as 700 subjects. It requires a strenuous effort to keep their personhood in mind and a vigilant external force to assure it. This distancing happens to everyone who has undertaken a clinical study. Only if we are mindful of this set of forces can we hope to avoid the gradual fading of subjects’ identities. When this happens, trouble awaits.

2. Searching for solutions on the cheap

From the time it was first described in Australia a century ago, lead toxicity in children has inspired controversy. Over the same period, the definition, dimensions and very nature of the disease have evolved.

The Australian medical community initially disputed the very existence of the disease [5]. Then, after its reality was accepted, it was believed that children who did not die during the acute illness were left without any residua. Sixty odd years ago, it was established that survivors suffered long-term effects [3]. Children who had recovered and who were thought to be asymptomatic were shown to be impulsive, aggressive and cognitively impaired. These deficits were believed to be suffered only by those children who had displayed clinical signs of encephalopathy. In the 1970s and 1980s, considerable evidence emerged showing that clinically silent lead burdens were associated with decrements in cognition, attention and school performance [6]. More recently, epidemiological data were published, which validated parents’ frequent reports that their children became hard to manage and were often violent after recovery from the acute illness [4,9].

As the clinical picture of lead poisoning evolved, so did the understanding of the causal roots of the disease. In the first half of the last century, it was thought that exposure was the product of a perverse habit, pica, and that this was due in part to maternal neglect. In the 1960s, the civil rights movement focused attention on the cities and minorities. The association of lead toxicity with the many assaults of poverty, for example, poor nutrition, decayed housing and burning of battery cases, became visible. The central culprit now became lead in the wrong place: where children could reach it. Blaming children or mothers diminished but did not disappear.

In the 1970s, a number of studies of asymptomatic lead exposure showed behavioral and cognitive effects [8]. The

threshold defined for toxicity was lowered, and as a result, the risk group for toxicity broadened. In 1998, DHHS/ATSDR reported that lead exposure was associated with low family income, race and urbanization: 36% of low-income urban White and 67% of low-income Black children had elevated blood lead levels. For White children with higher family incomes, the proportion was 12%, for Black children, the rate was 38% [1]. The fact that one White middle-class child in eight was at risk for lead toxicity was powerful news. On the cover of *Newsweek*, and on the inside pages of *Time*, pictures of White children surrounded by peeling paint appeared. Lead no longer was seen as purely a ghetto disease.

In 1991, the Department of Health and Human Services, in response to the resultant public outcry, published a truly revolutionary policy statement calling for the eradication of childhood lead poisoning. Federal policy, with the publication of this document, moved abruptly from case finding to authentic primary prevention. The report, “A Strategic Plan for the Elimination of Childhood Lead Poisoning” [10], asserted that “a society-wide effort could virtually eliminate this disease as a public health problem in 20 years.” A cost–benefit analysis in the report pointed out that while the costs for abating houses built before 1950 was US\$34 billion, the monetized benefits was US\$62 billion. There was, one could see, a bottom line profit to be earned by doing the right thing.

The publication of the “Strategic Plan” produced a surge of energy, optimism and commitment to wiping out the disease. No longer was lead poisoning seen as an unavoidable and intractable burden for an unheeded minority. It was clear that the enormous expense of abatement was dwarfed by the size of the benefits that would accompany the completion of the work. This silenced, at least for a while, the plaint of those critics who said that we could not afford to take on the job. Millions of our children were seen to be living in the middle of a poisonous surround. The threat was easy to identify; we knew how to get rid of it; and that while it was an expensive job to do, we would pay a larger penalty for not doing it. The price tag was irrelevant. It seemed possible that we could do well while doing good.

This prospect rapidly aroused opposition from a number of quarters. The traditional enemies of lead control played their traditional part. The Lead Industry Association, the International Lead Zinc Research Organization, the real estate interests and insurance companies chipped away at the plan as futile, expensive and a diversion of resources. Some entities not generally thought to oppose lead control played a negative role. The CDC and the Academy of Pediatrics withdrew their support for universal screening, permitting lead poisoning to be once again seen as a ghetto disease. The Alliance to End Childhood Lead Poisoning participated in a HUD-supported campaign to replace abatement with limited cleanup and patching of homes as the remedy for housing ills. In another publication, I have tried to delineate these actors [7].

It was not long before the vision of the early 1990s, true primary prevention, eradication of the disease in 15 years, was replaced by an enfeebled pseudopragsmatism. Instead of asking, “How can we develop a plan to spend US\$32 billion dollars over the next 15 years and eliminate *all* of the lead in dangerous houses?” the question became, “How little can we spend and still reduce blood lead levels in the short term?” Completely ignored was the fact that lead in excess is found in exactly the same place where jobs and decent housing are rare. That comprehensive deleading could at simultaneously create jobs, reduce unemployment and make the inner city livable, never occurred to the self-styled pragmatists.

In this climate, studies of different degrees of lead control, their relative efficacy and dollar costs became essential. The leading expertise about the sources of lead, its impact and the routes for children had for years been concentrated at the Johns Hopkins and the Kennedy Krieger Institute, and the City of Baltimore was burdened by some of the most heavily leaded housing in the country. The logical place to locate studies of the economics of lead abatement was obvious, and the studies begun.

Earlier in this piece, I said that what the Kennedy Krieger Institute group did might constitute a solecism. “Solecism,” that is, “a mistake, a blunder, an inconsistency” (OED). This is the most appropriate label for what happened in Baltimore. Most of us, if we are honest, will admit to having made mistakes in our investigations. What happened in the Tuskegee case was a crime. There is no resemblance

between the two. For the court to equate them was a rhetorical excess that approaches slander.

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