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Editorial

Epidemiology and the Effects of Radioactive Contamination: Time for a New Approach

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The science (and art) of epidemiology is arguably the most important area of human investigation in the modern world. The environment of human beings (and indeed all life) has been changed by human activity. There is an exponential trend in novel exposures that never existed in evolutionary history and which follow technological alterations of the biosphere that began about one hundred years ago. Epidemiology is the pre-eminent guardian of human health. We cannot do experiments on human beings, but human responses to harmful exposures resulting from changes in behaviour, culture and environmental contamination, must be the most important current issue. The proper study of mankind is man. Humans may be (in fact clearly are) at serious risk of harm, but nothing will be done by the political machine without evidence. Indeed we know, from large scale data that harm is increasing. Despite advances in medicine, and enormous investment in research, age specific cancer incidence rates increase, and recently we hear that lifespan in women is decreasing. Cancer is a primarily genetic disease and twins studies show that it is 80% environmental. (Epidemiological) studies show that sperm counts have been decreasing for many years. There are increases in diseases in children, and in young adults. The complex range of potentially harmful exposures in the modern environment seem to make any attempt to dissect out any particular agent appear formidable. Or so we are told. Yet there is no other option but to attempt the task. Because of their great lifespan and complex physiology human systems cannot be properly modelled by short-lived animals, even it seems in some cases for immediate toxicological effects. Somatic genomic damage, resulting potentially in increases in morbidity and mortality rates may take up to thirty years to manifest or even show only in descendants. But evidence is out there: it is the role of epidemiology to search it out and I particularly hope that this new journal will provide a platform for such independent epidemiological studies.

Some years ago I was the group leader in the work package for the science/ policy interface in a European Union project, the Policy Information Network for Child Health and Environment, PINCHE. The purpose of this collaboration of about 40 senior scientists, epidemiologists and toxicologists was to advise the EU Commissioners on how they could best determine policy in the area of limiting releases of harmful agents. The results of the deliberations have been published, and what we discovered and developed is important in the field of epidemiology. First there is an open secret: a big problem in this area is that studies of exposures to environmental contamination where there are economic or political consequences are rarely funded; or if they are funded, it is by organisations which have a stake in the outcome and this biases the result. All epidemiologists know how to do this: choice of study group and control group, selective exclusion of individuals in either group, selective use of multiple regression methods, boundary tightening/ loosening, choice of denominator. There is a whole spectrum of methodologies available to any researchers who might be employed to carry out directive or tendentious (now called—"positivist")

research. And anthropological "Science Studies" (see Bruno Latour) have long made it clear that scientists are not really different from other human groups in their ability to allow their personal history and culture to colour their approaches. PINCHE concluded that the way to assess risk of harm was to have oppositional committees where both sides of any issue were presented by research which was funded, what had been termed "red teaming".

Another issue emerging from PINCHE was peer-review. Studies informing on risk to human health are communicated through the peer-review literature. Those studies which reveal results which do not conform to the understanding of or scientific culture of, or position of the reviewers of a journal are usually swiftly rejected. I have seen many examples of important studies being rejected. The late Alice Stewart, who famously discovered the obstetric effects of gynaecological X-rays (40% excess risk of childhood cancer at 10mSv external dose), showed me several referee reports rejecting her 1990s analysis of the Japanese A-Bomb data which she had to send to 9 journals before the paper was accepted. I have to say, the hysterical responses by reviewers to her results, in some cases involving incorrect and absurd statements, made it clear that the reviews were not independent or unbiased. The reviewers of the major journals, the ones with the "top position" in impact factors, are (naturally) those who are top people in their fields: but these are just the people who have got to their positions by being part of (or often defining) the "scientific consensus". In such an environment there can be no new discovery. It is the priest and the madman, the Galileo problem.

Let me now move to discuss an area where all these issues have been paramount and to provide some examples of doubtful epidemiology which has resulted in grievous harm. This is the health effects of exposure to radioactive contamination, and specifically the health effects of living near a nuclear site which releases radioactivity to the local environment. In this field of study, epidemiology has historically been made subservient to physics, in a curious inversion of common sense which occurred over the period of development of nuclear weapons. Epidemiology basically needs two covariates: exposure and effect. The correlation between these defines the risk. The nuclear weapons testing was a period in which the stress covariate, the exposure, was defined as a new concept "absorbed dose" or dose. This was quantitative: energy per unit mass, and for external exposures to X-rays or gamma rays could be calculated or even objectively measured. And such a "dose" could be compared with natural radiation, though only for external radiation. For internal contaminations through ingestion or inhalation, the method was clearly faulty, and has been increasingly seen as faulty since at least 1980 when the nuclear site childhood leukemia clusters began to be discovered (by epidemiology).

There is now overwhelming evidence that childhood leukemia rates are significantly raised in those living near nuclear sites. The responses by government, by international risk agencies and by the nuclear industry-funded scientists are uniformly dismissive. The gold standard study for these people is the lifespan study of the Japanese A-Bomb survivors. Here, (external) "dose" was correlated with leukemia, and the relation was almost defined as a law of physics: it was certainly embedded into national law. Internal dose was ignored even though there was fallout and rainout. The effect of fallout and rainout (the famous Hiroshima "black rain", which was measured) could have been examined epidemiologically ("zero dose" controls versus all Japan) but it was not. On the basis of the simple relationship between "zero dose", medium dose and high dose, an excess relative risk was defined: it is thousands of times too low to explain the nuclear site child leukemias. But epidemiologically this is a false comparison. All three groups were exposed to internal contamination. The real control group is a truly unexposed group, which was, in fact, available in Miyagi Prefecture but the comparison has not been done. And so, on the basis of these "dose" arguments, the clear effects in the children have been dismissed as an interesting anomaly.

There are other epidemiological faults in the methods that have been employed by authorities to examine the nuclear site effect. Radioactivity is assumed by the studies to disperse radially from a point source, and groups of individuals are defined in terms of their radial distance from the site. This is clearly wrong, and was criticised in the report of the UK Government Committee Examining Radiation Risks from Internal Emitters (CERRIE, of which I was a member) in 2004. Releases are directional: through water to local sea or river with contamination of waterside or coast or through air to downwinders. No-one has attempted to examine this, even though there is no shortage of data.

The latest project is a proposed study of cancer near nuclear sites in the USA, directed by a committee chosen by the National Academy of Sciences. Looking at the discussions of the individuals on the steering committee of the study it is clear that the approach is again faulty, and the emphasis at the beginning on the statistical power of the study makes it clear that the project is being viewed though the external dose-based paradigm of the A-Bomb results, and not as an epidemiological study at all. Since the "doses" in the proximal radial ring are less than background, the committee begins by saying that it will be impossible to find anything at all.

But we know that epidemiology stands alone: results of a properly designed study give the results they give. The emphasis on child leukemia is based on the assumption that this is the only disease caused by radiation exposure. But that cannot be—indeed we know from the A-Bomb data that it is not. And since it is genetic or genomic damage that leads to cancer and leukemia, what is affecting the children will also affect the adults. But whilst with the children we are dealing with a vanishingly low

background rate, some 6 per 100,000 we can obtain far more statistical power concentrating on that recently increasing epidemic and unexplained scourge of the human race, breast cancer, where the background rate is about 150 per 100,000 (in England and Wales). Breast cancer is caused by radiation, and incidence has been increasing since the atmospheric nuclear test fallout of the 1960s. This is a much larger problem than child leukemia. What is the cause? Why not study that, and study it in the areas where the radioactivity released by the nuclear site is dispersed? This is what my colleagues and I have done. In this first issue of this journal I present studies of breast cancer near two of three nuclear sites in the UK which we have examined. Results support the belief that it may be the exposure to radioactive weapons fallout that is driving the breast cancer epidemic. I present these in the hope that they may assist the NAS committee to take a more measured and open view of how they might organise their approach.

Much definitive radiation epidemiology involves retrospective studies where the end points are cancer, but where a large proportion of the study group is missing or has died without a cause of death given. One example is the "US Radium studies". The results have been used to underpin the belief that internal exposures can be modelled by the "dose" approach. But up to 40% of those exposed to Radium before 1930 (the famous dial-painters) were either missing from the study group (assembled in 1952, 20 years after the exposures) or had no cause of death given. No epidemiologist should base any conclusions on such an analysis. Imagine trying to base a public health risk study on exposures to some toxin in a restaurant when half those who were exposed are missing? The end point of cancer involves quite small numbers on which to base an excess relative risk (in the case of leukemia in the US radium studies less than 9 cases in a study population of some 2000) yet hundreds of missing individuals (who died shortly after their exposures) fatally compromise the conclusions. The same criticism can be applied to studies of nuclear test veterans, to Chernobyl liquidators, Mayak workers, the list is long. A sample can only represent the population if it is randomly selected: if it is a population of survivors it is clearly biased. The Japanese A-Bomb studies are (as Alice Stewart showed) just such a biased healthy population as the groups were assembled 5 years after the exposure after the weak will have died.

Another built in assumption, which particularly affects modern computer-based epidemiology, is that complex (or even simple) regression methods give the right answer. Statistical comparisons (e.g. Mantel Haenszel) are now rarely seen, they are not clever enough: it is all regression nowadays. The built-in assumption here is that a dose response relation is linear, or monotonic and increasing. Enormous amounts of data show quite clearly that this is not the case: even in the area of the A-Bomb results (check out the colon cancer data points). Of course it is easier to model if there is a linear or monotonic increase in effect with dose but there is not. And simple considerations of biology will show that such a response is unlikely except over a narrow range. The most usual result is a dose response relation which is biphasic: up down and up again. If such data is plugged into a regression package, a low gradient straight line is fitted, defining a modest excess relative risk per dose. Even a superficial look at the data shows that this is not a valid description of what is happening. I refer you to the 15-country study of nuclear workers by Cardis et al of IARC. This shows high risks at the lowest doses, reducing at slightly higher doses and then increasing gradually to the highest doses. This happens so often in dose-based epidemiological studies that it is clearly a real effect. And there are (as Bradford Hill would demand) persuasive biological explanations for such a biphasic dose response. For example, take the foetus. As exposure is increased from the lowest dose, effects could be seen in the end point (e.g. infant leukemia). As the dose increases, the foetus dies (miscarriage, abortion) and the risk falls. The same is true for cells, where sensitivities change by 100-fold at certain periods of mitotic activity, and so there are two types of cell always present in clonal tissue, sensitive and insensitive.

To conclude, I would hope to see this new journal take a lead in becoming a home for reporting basic and accurate studies about, or providing reviews on, the increasing dangers from environmental contamination. If this is truly spaceship earth, then someone has to provide true and unbiased advice to the captain on what is happening. And don't wait for someone to fund you. You will be lucky if anyone does. There is enough historic data there to examine the hazards in the main areas, ionising radiation contamination, electromagnetic fields, mobile technology, water and air pollution, nanoparticles and so forth. And if the registries refuse to give out the data, as we see in the aneurysm paper published in this issue, complain. Or collect your own data using questionnaire methods as we did in the study presented in this issue. And publish your results here in this new journal: make it the flagship and home for messengers of bad (or maybe good) news about the biological consequences of human progress.