COMMENTARY

Understanding the Health Impacts of Nuclear Weapons Production in the Southern Urals: An Important Beginning

Scott Davis, Ph.D*

The carcinogenic effects of ionizing radiation have been studied more extensively than those of any other single chemical or physical agent. Radiation carcinogenesis has been investigated in laboratory animals of virtually every species at every level of biological organization. Numerous large, well-done, long-term epidemiological studies have documented a broad array of carcinogenic effects of ionizing radiation in different human populations under varied conditions of exposure. Different types and sources of radiation exposure have been investigated, and important potential modifying factors have been evaluated. It is notable, however, that much of our current understanding of radiation carcinogenesis in humans derives from comprehensive long-term follow up studies of a select few groups: survivors of the atomic bombings of Hiroshima and Nagasaki [1]; persons treated for tuberculosis with x-rays [2,3]; persons treated for ankylosing spondylitis with radiotherapy to the spine [4]; and women treated for cancer of the uterine cervix with radium implants or external radiotherapy [5].

These sentinel studies, as well as many of the smaller epidemiological studies of ionizing radiation reported to date, are limited because the exposures received generally resulted in relatively high doses, which were accumulated at relatively high dose rates. Although these studies have contributed greatly to our understanding of the biological aspects of radiation carcinogenesis and have been instrumental in early attempts to formulate guidelines for radiation protection, there is an increasing need to focus attention now on understanding the human health effects of much lower doses of ionizing radiation and of protracted low-dose exposures (i.e., low dose rates).

Indeed, it is within this low-dose context that most people are concerned about radiation exposures. Occupational and population radiation protection standards have generally been derived from extrapolating the experience at high doses to the low doses more typically encountered today. The wisdom of this approach and the assumptions inherent in these extrapolations are being increasingly questioned and challenged. At present, there remains considerable uncertainty and debate regarding the carcinogenic effects in humans of low doses of ionizing radiation and the appropriateness of the various extrapolation models used. There is considerable evidence from animal studies, for example, that the carcinogenic effectiveness of low-linear energy transfer (LET) radiation is reduced at low dose rates. Available evidence in humans is thus far insufficient to confirm this notion or adequately to quantify or describe the nature of a postulated dose rate reduction factor.

In efforts to address this gap in understanding, considerable effort has been made in recent years to begin to identify and assess health effects in groups and populations exposed to low doses of radiation [6]. Radiation exposures studied in this context include occupational sources, diagnostic radiography, natural background radiation, fallout from nuclear

0051-2438/1992/0204-0216$03.00/0

* SD is Associate Member, Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, and Associate Professor, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington. Address correspondence and reprint requests to Scott Davis, Ph.D., Fred Hutchinson Cancer Research Center, 1124 Columbia Street, MP474, Seattle, WA 98104.

weapons testing, and emissions from nuclear facilities. In particular, considerable attention has been devoted to the latter two sources: studies of populations exposed to radiation released as a consequence of nuclear weapons production or testing, and nuclear power production.

Such studies are exceedingly difficult to conduct. In most instances it is not feasible to quantitatively assess or estimate radiation doses received by individuals, either because there is insufficient information to allow the reconstruction of doses retrospectively, or because access to the necessary information is compromised by the environment of secrecy that has so long characterized the nuclear industry worldwide, or both. Furthermore, it is often difficult, if not impossible, to identify accurately, the appropriate population at risk to study and it is more difficult still to ascertain the health status of individuals in that population. Even when these formidable problems can be overcome, the ability to detect small increases in cancer occurrence associated with low-level radiation exposure is likely to be close to or beyond the limits of most epidemiological studies. Thus, with a very few notable exceptions (e.g., studies of persons exposed to fallout from nuclear weapons testing in the Marshall Islands [7]), most such investigations to date have been limited to geographical studies that attempt to relate disease rates to surrogate indicators or correlates of presumed radiation exposure. Whereas results from these studies may provide some general direction in understanding low-dose effects, they are incapable of contributing substantially to our knowledge of human carcinogenesis at low doses or dose rates.

In the last six years, however, we have begun to witness the emergence of a new generation of studies that hold the promise of being capable of advancing our understanding in this area. These investigations have been enabled largely as a result of newfound freedoms of informational exchange worldwide. In the United States, vigorous expansion of earlier studies of persons exposed to radiation fallout from atmospheric testing of nuclear weapons in Nevada, with the addition of rigorous reconstruction of individual doses, has resulted in provocative findings of increased risks of leukemia [8] and thyroid cancer [9] associated with relatively low radiation doses. Revelations in 1986 of substantial atmospheric releases of radioactive materials (largely radioactive iodine) from the Hanford Nuclear Site in eastern Washington State in the late 1940s and 1950s have led to the funding of a comprehensive dose reconstruction project designed to produce individual dose estimates and a parallel epidemiological cohort study of thyroid disease in persons exposed [10]. Similar dose reconstruction projects are now underway at a number of other U.S. Department of Energy nuclear facilities, and additional epidemiological studies are being contemplated. In the United Kingdom, access to monitored radiation doses of workers at the Sellafield Nuclear Plant enabled an epidemiological analysis that suggests that extremely low preconception radiation doses to fathers are associated with an increased risk of leukemia in their offspring [11]. Several attempts are currently underway to expand on and confirm these findings.

Unparalleled, however, in this new generation of research are recent activities in the former Soviet Union. Since the explosion at the Chernobyl Nuclear Power Station on April 26, 1986, a new chapter in the investigation of population exposures to ionizing radiation has been opened. What began initially as attempts largely by investigators outside the former Soviet Union to assess the potential health impacts of fallout from the accident in western Europe and subsequently North America and other parts of the world have evolved into numerous collaborative international efforts to investigate health impacts among populations exposed within the boundaries of the former Soviet Union itself. This has been a formidable task, given decades of control and secrecy and the increasing scarcity of resources. Although considerable effort has been made by formerly Soviet investigators to assess and estimate radiation doses and to establish surveillance systems for long-term follow-up and diagnosis of persons exposed, precious little has come of these efforts thus far in terms of completed or published studies describing either the radiation dosimetry or cancer risk. The potential for scientific advances remains great, and it is the fervent hope of many that the obstacles of a historically closed and secret bureaucracy, scarce resources, and the inevitable challenges of international collaboration can be overcome to produce meaningful results.

Kossenko and colleagues [12] report in this issue of *The PSR Quarterly* results regarding the risk of leukemia associated with low-dose-rate population exposures to ionizing radiation in the Chelyabinsk region of the southern Urals in eastern Russia. In an accompanying commentary, Amundson [13] describes the overwhelming magnitude and extent of the radiation contamination that took place over more than a decade in the late 1940s and 1950s and the suffocating effects on scientists and the populace at large of more than 40 years of secrecy surrounding these events. Undoubtedly, the widespread concern for human health around Chernobyl and the increasing openness that has evolved from the research and humanitarian activities that have been initiated in that region, in combination with a rather fortuitous timing of events that have led to the restructuring of the former Soviet Union, resulted in the recent revelations of what took place near Chelyabinsk.

Kossenko's work is unprecedented and should be evaluated in the broader context reviewed briefly in the paragraphs above. Her stated purpose was to study low to moderate radiation doses delivered at low dose rates in a relatively large and stable population. She restricted the investigation to a consideration of exposures resulting from radiation released into the Techa River from 1949 to 1956. Kossenko had access to (and was largely responsible for developing) a unique set of resources and information: the source term was relatively well characterized (i.e., what types of materials were released, where, how much, and when); environmental monitoring data existed and appear to be reasonably comprehensive; cohorts were identified largely on a geographical basis to correspond with what was known about the pattern and dispersion of the contamination; medical and follow-up evaluations were conducted in these populations from early on, beginning in 1951, and have continued on a regular basis; sources of and access to medical care have been relatively uniform and stable in the region during the period of follow-up; and the population has been reasonably stable as well, with minimal in-and-out migration. An additional, but somewhat perverse, advantage of the local situation was that the population at large was essentially uninformed about the radiation contamination and their own exposures, thus eliminating the possibility that widespread interventions or behavioral changes would have materially affected the opportunity for exposure.

Kossenko and her colleagues attempted to estimate radiation exposure from both external and internal sources. To characterize external exposures, they used three sources of data. They had information on the releases into the river by time and major component. They also had information on gamma dose rates by distance from the river for individual years from 1951 to 1954 in a number of specific areas along the river (e.g., specified areas of villages and inside homes). Combining this information, they estimated average exposure levels by area along the river for 1951 to 1954. They also had survey information about lifestyles in the villages along the river in different age groups (e.g., time spent indoors versus outdoors, time spent in various activities). They used these data, in conjunction with the exposure levels, to estimate annual average doses by village by age group. It is not clear how the years before 1951 (the first reactor began operation in June 1948) or after 1954 are accounted for, although it appears that exposures only through 1956 were considered.

Internal exposures were estimated by using two sources of information. Beginning in 1960, surface beta activity in tooth enamel was measured, and, since 1974, 12,000 people who were exposed in the early 1950s and who remained in the area had whole-body count determinations of ^{90}Sr and ^{137}Cs depositions. From these data, age-dependent models were developed to estimate strontium retention in bone. Through the use of additional information on ^{90}Sr content in bones from people in "other regions" as well as data from ^{85}Sr injection experiments, red bone marrow and bone surface doses were reconstructed. In addition, by using data from the tooth measurements, rates of ingestion of strontium as well as other radionuclides were estimated. Although a number of technical questions remain unanswered at this juncture about how this work was done (e.g., which and how many people provided teeth, how sensitive and reproducible the measurements are, and how the measurement and exposure time periods correspond), laborious efforts were made to utilize extensive human measurements in estimating internal doses. For final epidemiological analysis, the external and internal estimates were combined to estimate mean red bone marrow dose by village and average cumulative organ doses (for four additional organ groupings) in four selected villages.

Results regarding leukemia risk are presented for incidence and mortality outcomes separately. Incidence findings suggest an approximate twofold increase in risk in the "exposed" population compared with two separate control groups. The first control group represents what might be considered a regional control as it encompasses all rural districts in the Chelyabinsk region except the four irradiated districts (which presumably constitute the "exposed" group, although this is not completely clear). Persons in this group were born before 1953 and number 343,000. Leukemia was ascertained between 1972 and 1982.

The second control group consisted of 52,000 people in two rural districts along the Techa River that were "unexposed." This group is presumed to be a closer match to the exposed districts regarding the quality of medical care, the geography, and ethnic composition. Leukemia was ascertained in this group from 1952 to 1958. Although details of case ascertainment and the characterization of exposures in the different areas are not well described and follow-up periods are different, the incidence risk estimates appear to be reasonably internally consistent.

The mortality results are more difficult to understand and interpret. Mortality from leukemia, on the basis of death certificate entries, is compared among a number of different exposed and unexposed groups. These groups are not well defined, and it appears that doses *decrease* with increasing duration of residence. Results in Table 5 of Kossenko et al. [12] indicate that death rates from leukemia are substantially higher (two- to fourfold) in the exposed relative to the control areas.

Overall, the findings indicate that there is an increase in leukemia in populations living along the Techa River that would have been exposed to the radiation releases from Mayak. As presented, the excess of leukemia arose between five and 20 years after initial exposure, and there is some indication of a dose response (i.e., increase in risk with increasing dose). The results also suggest a lower than expected rate of leukemia, given the doses estimated. Whether this constitutes evidence of a dose-rate reduction is of great interest, although it is unresolved by the present report.

This is the first published account of work to emanate from the truly unique resource established in Chelyabinsk and is the first assessment of cancer risk related to the widespread radiation contamination in the region. It is a remarkable piece of work, especially given the obstacles the investigators have faced through decades of secrecy and the increasing shortage of resources. However, like all epidemiological studies, it is not without its shortcomings and limitations. Probably chief among them is that this study is not truly an individual follow-up study based on analyses of individual outcome determination and radiation dose estimates. It is somewhat a hybrid of a geographical and cohort study combined. The principal mechanisms of case finding appear to be population based and related to a relatively well-defined and stable population (cohort?). Dose estimates are based in part on biological measurements of a large number of individuals from this same population. Nonetheless, the assignment of exposure or dose category and the comparison of outcomes are largely ecologically based. Thus, there is still much that can likely be learned from this basic data resource regarding the risk of leukemia in the Chelyabinsk region. Future work should strive toward achieving the goal of obtaining individual-based risk estimates that will allow for a better characterization of the dose response at low to moderate doses.

Thus, it seems that the most appropriate interpretation of this work at present is to consider it a very important beginning. Judging from what we have learned in the recent few months about what took place in the region, this report is but one small piece of what lies ahead to be investigated. The Techa River releases constitute only a portion of the radiation exposures that have likely occurred to large numbers of people. The storage tank explosion in 1957, the atmospheric dispersion from Lake Karachay, the subsequent river exposures after 1956, and the open question of continued exposures from ongoing operations of the Mayak facility need to be investigated.

The data reported thus far are limited to a few long-lived radionuclides (principally ^{90}Sr and ^{137}Cs). What might be learned about exposures from other sources that could have substantial health impacts, such as radioactive iodine? Might it be possible to reconstruct thyroid doses from available records? The present report is also limited to one specific outcome: leukemia. Clearly, with such widespread exposure to such large numbers of people, the opportunity exists to investigate a broad spectrum of radiation-induced disease, including other types of cancer, benign tumors, reproductive outcomes, and acute effects. With the resources developed thus far, it should be possible to include in such studies the collection and storage of biological material for molecular and genetic studies of radiation-induced damage.

This work is also just the beginning in terms of the potential to include other study populations and exposures. The resource developed thus far at Chelyabinsk is focused principally on the regional population. There also exists a work force that has been in place for over 40 years and that may have been quite substantial in number. Occupational exposures to radiation clearly occurred and may be reasonably well documented and recorded. In addition, the region around Chelyabinsk is heavily industrialized. It might be possible to begin to investigate the relationship between other important occupational exposures and ionizing radiation in relation to cancer induction.

Kossenko and her colleagues are to be congratulated on providing a very provocative and timely set of results. They have probably raised more questions than they have answered. It is hoped that this will serve to initiate an active scientific exchange of new ideas, criticism, and collaboration to exploit fully the unique resources so painstakingly developed over several decades. Whereas the human toll of the events near Chelyabinsk may turn out to be unprecedented, so too may be our gains in understanding the biological effects of ionizing radiation. ❧

REFERENCES

1. Shimizu Y, Kato H, Schull WJ. Studies of the mortality of A bomb survivors. Report 9. Mortality, 1950–1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 1990;121:120–141.
2. Miller A, Howe G, Sherman G, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. N Engl J Med 1989;321:1285–1289.
3. Hrubec Z, Boice JD, Stovall M, et al. Breast cancer after multiple chest fluoroscopies: second follow-up of Massachusetts women with tuberculosis. Cancer Res 1989;49:229–234.
4. Darby SC, Doll R, Gill SK, et al. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987;55:179–190.
5. Boice JD, Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 1988;116:3–55.
6. National Research Council. Health effects of exposure to low levels of ionizing radiation. BIER V. Washington, D.C.: National Academy Press, 1990:371–389.
7. Hamilton TE, VanBelle G, LoGerfo JP. Thyroid neoplasia in Marshall Islanders exposed to nuclear fallout. JAMA 1987;258:629–636.
8. Stevens W, Thomas DC, Lyon JL, et al. Leukemia in Utah and radioactive fallout from the Nevada test site. JAMA 1990;264:585–591.
9. Stevens W, Till JE, Thomas DC, et al. Report of a cohort study of thyroid disease and radioactive fallout from the Nevada test site. Report to the National Cancer Institute, University of Utah, July 1992.
10. Gilbert RO, Simpson JC, Napier BA, et al. Statistical aspects of the Hanford Environmental Dose Reconstruction Project and the Hanford Thyroid Disease Study. Proceedings of the American Statistical Association Conference on Radiation and Health. Ionizing Radiation Risks: Present and Future. Radiat Res 1990;124:354–355.
11. Gardner MJ, Snee M, Hall AJ, et al. Results of case-control study of leukemia and lymphoma among young people near Sellafield Nuclear Plant in West Cumbria. Br Med J 1990;300:423–429.
12. Kossenko MM, Degteva MO, Petrushova NA. Estimate of the risk of leukemia to residents exposed to radiation as a result of a nuclear accident in the southern Urals. PSR Quarterly 1992;4:187–197.
13. Amundson B. Scientific integrity and adequate health services: twin casualties of the nuclear arms race. PSR Quarterly 1992;4:210–215.