Secrets of the a-bomb survivors: the long-term effects of the bombs are still unclear, as doctors try to pin down how radiation causes disease

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FIRST there was a blinding flash of white light, followed just a second later by the shock wave that smashed into the factory in which Shotaro Kodama was working. "Then everything became dark, because of the dust. Part of the ceiling fell in. I ran outside and saw that houses were broken and damaged. The schoolhouse was smouldering. I don't know how long it was after the explosion, but wounded people started arriving looking for water. They were badly burnt. It was awful to see."

Kodama was 15 years old when the Enola Gay dropped its 4000-kilogram uranium bomb just 2 kilometres away, over the centre of Hiroshima. Shielded inside the factory, Kodama was one of the fortunate ones. But he lost an aunt, an uncle and cousins. "Many relatives were killed by the atomic bomb," he says.

More than 150,000 people are thought to have died when the bombs fell on the Japanese cities of Hiroshima on 6 August 1945, and on Nagasaki three days later. Yet surprisingly, 45 per cent of the 280,000 or so people who survived their initial exposure to radiation 60 years ago are still alive today, and they have become the subjects of the largest study ever conducted into the long-term effects of radiation exposure.

We now know that exposure increases the long-term risk of cancer, and that for solid turnouts, the risk lasts a lifetime. Studies show that unborn children exposed to radiation grow up to be on average smaller and less intelligent than their peers, that the increase in their risk of leukaemia peaks after 10 years, and that radiation appears to hike the risk of other diseases.

But there is still much we do not know. "We still have no clear answers as to how the A-bomb radiation has caused biological effects in humans," concluded a review published last spring by a team from the Radiation Effects Research Foundation (RERF), based in Japan. It is also not yet clear whether the children of the A-bomb survivors might have inherited their parents' greater propensity to ill-health.

RERF is the organisation best placed to find out. With about 150 researchers in Hiroshima and Nagasaki, and funding from the US and Japanese governments, the foundation, and its predecessor, the Atomic Bomb Casualty Commission, has been closely following the health of survivors and their children since the 1950s.

The earliest medical studies focused on acute radiation exposure. By 15 September 1945, the Japanese government had already set up a special committee to investigate Hiroshima and Nagasaki "with the full scientific capacity of our nation"--although the results of this research were not published until 1951. But on 6 July 1946, a paper appeared in The Lancet describing the horrors of "atom bomb disease". The first symptoms to appear were anorexia, nausea and vomiting, followed by failure of the bone marrow to efficiently make blood cells, and eventually, death. Pregnant women within 2 kilometres of ground zero miscarried, the paper reported, or gave birth to premature babies who died soon after.

Later studies revealed the effects of radiation exposure on some of the roughly 3000 people exposed while in the uterus, but whose mothers had been further away from the blasts. IQ tests in the 1950s showed the scores of those whose mothers had received a typical dose of 0.2 sieverts were down by an average of five points. Those subjected to higher doses were more likely to suffer learning difficulties--but the work also revealed that the worst time for a fetus to be exposed was 8 to 15 weeks after conception. Another study, published in the journal
Radiation Research in 2002 (vol 158, p 346), found that children exposed in the womb grow up to be shorter than their peers.

The A-bomb survivors provided the first significant insights into the immediate effects of radiation exposure. But the true picture of the long-term effects is still emerging.

RERF's ongoing Life Span study of more than 100,000 residents of Hiroshima and Nagasaki has already revealed vital information about the relationship between radiation and cancer. The estimates for increased risk have been refined over the past 30 years. Data published in 1996, covering 1950 to 1990, showed that in that period, half of the leukaemia deaths and 7 per cent of deaths from other types of cancer in the two cities were caused by A-bomb exposure. With solid tumours, the increased risk was higher for stomach, colon, lung and breast tumours. All the figures show a strong association between the size of the dose and the size of the increase in risk.

Recent lab studies prompted by the epidemiological cancer data are also throwing new light on the underlying biology. And it seems that some people might be more genetically susceptible to developing leukaemia following radiation exposure.

To date, 203 survivors who received an acute minimum dose of 0.005 Sv of radiation (that is, everyone within about 2.5 km of ground zero of each bomb--see "Two bombs, same effects", page 8) have died from leukaemia. About half of these deaths are thought to be have been caused by exposure to radiation from the bombs. Early genetic studies of the survivors showed clearly that radiation causes translocations of genetic material within chromosomes. But because this damage is essentially random, it has been tricky to explain how radiation might create the specific translocations in multiple cells needed to trigger leukaemia.

Recent research has identified a subset of about 5 per cent of people in the general population who have relatively large numbers of pre-leukaemic cells, which carry the specific translocations associated with the disease. In a paper published earlier this year in Radiation Research (vol 163, p 258), Nori Nakamura, RERF's head of genetics, suggests that additional translocations caused by radiation exposure tipped the balance for at least some of this susceptible subset of A-bomb survivors. "This is just a hypothesis," Nakamura stresses. But his idea is that they were the only people at real risk of developing leukaemia after the bombs were dropped. Once they had developed the disease, the remainder had the same statistical risk as everyone else--which explains why the risk for survivors is now the same as for people who haven't been exposed to radiation, say Charles Waldren, chief of research at RERF.

There are other unanswered questions about radiation-induced cancer risks. No one really understands the precise nature of the dose-response curve for radiation-induced cancer for doses of 0.1 Sv or less. This remains a controversial area of research, but it may be that a threshold for radiation exposure, below which there is no increased cancer risk, does not exist, says Waldren. And that means there may be no safe dose of radiation.

But while we have known about the fundamental link between radiation exposure and cancer risk from the A-bomb survivor data for decades, recent RERF studies also suggest that acute radiation exposure might raise the long-term risk of other sorts of diseases, including chronic liver disease and thyroid disease. Research published last year (Radiation Research, vol 161, p 622), analysing data from 1958 to 1998, reveals an increased risk of high blood pressure and heart attack for Hiroshima and Nagasaki survivors aged under 40 when the bombs were dropped.

However, researchers are not clear on the biological explanation. "Details of mechanisms by which radiation exposure increases the risk of cancer are largely unknown, but there is a plausible mechanism that it causes certain kinds of mutations known to cause cancer," says Waldren. "But when it comes to non-cancers, while many
statisticians believe it, most biologists are dubious, frankly. They are not clear about how radiation could cause these non-cancer diseases.

There is no shortage of suggestions, based largely on the studies of long-term effects on the immune system. Radiation damages bone marrow, and the fall in levels of red and white blood cells can kill (see "Treating the victims", page 7). Kodama's white blood cell count dropped immediately after the blast. "I got infections that took a long time to heal. But there are some survivors who still suffer infections very easily. The doctors say there is no cause. But I think it is related to the A-bombs," he says.

Medical studies of survivors back up Kodama's theory. Blood tests showed that for most, white blood cell production returned to near normal several months after the blasts, but a 2004 RERF report concluded that the immune systems of some survivors who received relatively high doses of radiation still bear the scars. Evidence includes radiation-induced changes to the DNA within stem cells that produce blood cells, resulting in lower than normal numbers of helper T-cells, for instance. These effects are small, and it's far from proven that they might increase susceptibility to any particular disease, though, the report adds: "nevertheless, it may be possible".

In research published in the American Journal of Medicine earlier this year (vol. 118, p 83), RERF's Kei Nakachi and colleagues also reported an increase in markers of inflammation in blood, such as immunoglobulin levels, in 440 survivors from Hiroshima. A study published four years earlier in the International Journal of Radiation Biology (vol 77, p 475) found a significant association between persistent low-level inflammation among A-bomb survivors and their radiation dose. Inflammation has already been implicated as a risk factor for atherosclerosis and heart attack. A weakened immune system might also leave the body more open to microbial infections.

RERF is now calling for collaborations with other teams around the world, to study in detail the millions of pathology samples collected from survivors and to probe the mechanisms for explaining radiation exposure and disease, while also improving our understanding of the impact of radiation on the genome.

In fact, some of the most valuable information about the lifetime health risks of radiation exposure is yet to come. Cancers are more common in old age, and more than half the cancers expected among the survivors have yet to appear. The next 20 years will reveal clues about the link between radiation and other diseases, and whether the children of survivors have inherited some of their parents' cancer risk.

Thankfully, epidemiological research on 22,000 children, about half of whom had a parent who was within 2 kilometres of ground zero, suggests not. Genetic studies have also failed to find evidence of inherited radiation related mutations. One study of offspring led by Nakamura and published last year (Radiation Research, vol 162, p 250) found no evidence that A-bomb radiation had any effect on a set of highly variable regions of DNA known as mini satellite loci within the sperm and egg cells of their parents. If radiation had caused ongoing germ cell damage, the idea is that these regions would be the ones to show it.

It is still too soon though to be certain that the survivors' children are in the clear. Their average age is still just 48--too young for most cancers to appear. "We're going to learn as much in the next 20 years as we have in the past 60," says Waldren.

RELATED ARTICLE: Treating the victims.

Dr Kenjiro Yokoro was a first-year medical student in Hiroshima in 1945. Evacuated just 10 hours prior to the bombing, he returned three days afterwards, on 9 August. "I was asked to assist doctors at a relief station in a burnt ruin of a hospital 1.2 kilometres from the hypocentre. Many of the victims visited the relief station every day.
And many of them had a severe reduction of white blood cell count, due to devastation of haematopoietic tissue in bone marrow," Yokoro told New Scientist. "Many succumbed from infectious diseases. These victims lost their defence power, so bacteria and viruses invaded freely."

Ionising radiation can damage any cell in the body, but rapidly dividing cells are hit the hardest, so stem cells that produce blood cells in the bone marrow are especially vulnerable. Radiation doses between 2 and 8 sieverts can damage blood cell production, and kill you. The loss of white blood cells leads to opportunistic infections and loss of platelets leads to haemorrhaging.

A team at the Armed Forces Radiobiology Research Institute in Bethesda, Maryland, is investigating blood-boosting drugs that could be given to an entire city in the event of a terrorist nuclear attack. Their most promising drug to date is 5-AED, which stimulates production of a range of growth factors that boost blood cell creation. "5-AED is relatively inexpensive, has extremely low toxicity, and is quite stable at environmental temperatures, meaning it could be easily stored and used by large numbers of people without physician supervision," says Hark Whitnall, head of AFRRI's Radiation Casualty Management Team.

AFRRI is also investigating drugs that might reduce the long-term risk of cancer. One project involves targeting genetic changes caused by radiation exposure. For instance, animal tests have shown that low levels of radiation trigger cancer-causing mutations in the ras gene, and these can be tackled with a drug called buthionine sulfoximine.

Diet might also be important, if only for helping to reduce absolute cancer risk. Last year, Catherine Sauvaget of the National Institute of Public Health in Wako, Japan, reported that A-bomb survivors who ate fruit or vegetables daily between 1980 and 2000 were 13 per cent less likely to die of cancer in that period. However, this figure is similar to that found in other research on the general population. It's still not clear whether radiation survivors could gain any additional benefit from a diet high in antioxidants, Sauvaget says.

But AFRRI studies show that taking antioxidants before exposure can protect against radiation damage. Ionising radiation triggers production of free radicals within cells. The idea is that the antioxidant vitamin E might reduce cell damage by mopping up the free radicals in the immediate aftermath of exposure. And animal tests do show that high doses of vitamin E can indeed protect against otherwise lethal doses of radiation.

The institute is also collaborating with companies producing nutritional supplements to create a supplement with immune-boosting and antioxidant properties, which could be given to military personnel to help protect them against future exposure. Emma Young

RELATED ARTICLE: Two bombs, same effects.

Little Boy, which exploded half a kilometre above Hiroshima, contained 60 kilograms of uranium-235. Fat Man, which devastated Nagasaki, was packed with plutonium. Both bombs blasted out gamma rays and neutrons. And the residents of both cities have the same radiation-related health risks, according to how far away they were from the exploding bombs.

People very close to ground zero died from the blasts. The majority of those who survived the blast itself, but who lived just 950 metres from the hypocentre, were exposed to 4 sieverts or more of radiation, and died as a result. People just 50 metres further away were more lucky, receiving 3 Sv, while those 100 metres further away received 2.5 Sv. Most people who received 3 Sv or less survived. "So a difference of just 100 metres or so determined living or dying," says Charles Waldren, chief of research at RERF. At both sites, anyone within a radius of about 3
kilometres was affected.

To chart accurately the health risks of radiation exposure, though, it’s vital to know exactly how much of each type of radiation was released by each bomb. Sixty years after the blasts, estimates are still being refined.

The most recent reassessment of the bombs’ output was completed in 2003. The calculations are based on a host of new data, including a survey of levels of a rare isotope of copper, created during exposure to fast neutrons (Nature, vol 424, p 539). The new assessment upped the levels of gamma rays delivered to each city by about 10 per cent. It concluded that Himshima and Nagasaki received roughly equivalent gamma-ray doses—an average of about 0.2 Sv for people within about 3 kilometres of the blasts (compared to a background average of about 0.003 SV per year).

The new estimates suggest that people in Hiroshima were exposed to three times as much neutron radiation as those in Nagasaki. The total neutron doses were much smaller than the gamma ray levels, however, at about 0.01 Sv for Hiroshima, and 0.003 Sv for Nagasaki.

These figures take into account that neutrons are about 10 times as "biologically effective" as gamma rays—in other words, they do about 10 times the damage. "However, there is uncertainty about neutron effectiveness. Some researchers argue that neutrons are 100 times more biologically effective than gamma rays," says Hark Little, an epidemiologist at Imperial College London, who has worked on the A-bomb data.

But, says Waldren: "I think, for sound biological reasons, that times 10 is a much better estimate for cancer induction, and even that may be too high. This is another case of disagreement between statisticians and biologists," he says.

In any case the 2003 increase in the gamma ray estimates does affect the cancer predictions. Last year, a RERF team reported that, because we know now that the A-bomb victims received higher doses of radiation than once thought, the estimates of solid-cancer risk per sievert, and the leukaemia dose-response curve, should both decrease by about 8 per cent. Emma Young

RELATED ARTICLE: Chernobyl contamination worsens.

Nearly 20 years after Chernobyl split open and spewed radioactivity across Europe, the contamination is actually getting worse. The area of Belarus that was badly polluted by cancer-causing alpha radiation from the accident has more than tripled since 1986.

Radiation levels will remain high for 270 years and continue to endanger the health of local people for generations, says a study by Belarusian scientists. Rural communities eating contaminated mushrooms and berries will be most at risk, they warn.

When reactor four at Chernobyl in the Ukraine exploded on 26 April 1986, among the many radioactive isotopes it showered over Belarus was plutonium-241. This has a half-life of 14.4 years, emits beta radiation and decays to americium-241, which emits alpha radiation.

According to the National Academy of Sciences in Gomel, Belarus, the decay of plutonium-241 into americium-241 will expand the regions seriously contaminated with alpha radiation from 950 square kilometres in 1986 to 3500 [km.sup.2] in 2006. Alpha radiation levels are expected to remain more than twice as high as they were immediately after the accident until 2276.
The contamination, which is scattered in patches across the south and east of Belarus, ranges from 740 to 3700 becquerels per square metre, the study says. This is between 14 and 70 times as high as the average for the whole of the country (Journal of Environmental Radioactivity, vol 83, page 49).

The researchers, led by Vladimir Knatko from the Academy's institute of Radiobiology, are concerned that the impact on the health of people in Belarus may have been underestimated. Alpha radiation from americium-241 is more dangerous than beta radiation, they argue, because alpha particles inside the body can trigger malignant tumours, with those who ingest the most at greatest risk.

The growing threat from alpha radiation is the latest in a series of discoveries which are prompting scientists to rethink the risks from the aftermath of Chernobyl. Keith Baverstock, a radiation scientist from the University of Kuopio in Finland, says there have been "hints" that chronic exposure to low levels of caesium-137 from the accident could be accelerating the development of cancers.

He also highlights studies that have suggested an increase in mutations in germ line cells in children whose parents were exposed to radiation in Belarus (New Scientist, 27 April 1996, p 6). "This does not fit into the conventional radiological protection framework," he says. "The questions seem to be arising faster than the answers."

Baverstock, who used to be a radiation adviser with the World Health Organization, was instrumental in uncovering Chernobyl's largest unexpected health impact. An authoritative study from the international Agency for Research on Cancer in Lyon, France, has recently confirmed that iodine-131 from the accident triggered as much as a 90-fold increase in thyroid cancers in children (New Scientist, 21 May 2005, p 7).

Chernobyl has also sprung surprises where animals are concerned. Radiation from the accident has doubled germ line cell mutations in barn swallows (Hirundo rustico), US and French researchers will tell a conference in Montreal next week. Survival rates among adult birds in the Chernobyl region have halved, they will announce.

Murdoch Baxter, the founding editor of the Journal of Environmental Radioactivity, points out that Chernobyl's caesium-137 has persisted in soil for much longer than expected. It keeps being recycled into grass and plants, he says, which explains why sheep at hundreds of farms in the UK are still subject to restrictions on movement and slaughter. Rob Edwards

EFFECTS OF THE A-BOMB Cancer and leukaemia mortality rates, 1950 to 2000 Exposure
Solid age Cases Deaths Survival cancer Leukaemia
0-9 17,833 1,845 80% 562 41 10-19
17,563 4138 76% 1446 47 20-29
10,891 4401 60% 2344 58 30-39
12,270 9,508 23% 2344 59 40-49
13,503 13,249 2% 2555 58 50+ 14,551 14,544 0% 1,820 30
Total 86,611 47,685 45% 10,127 296

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