Fallout and cancer: The debate goes on

Did fallout from nuclear-weapons tests conducted in Nevada during the 1950s and 1960s contribute to a higher-than-normal incidence of cancer for downwind populations in Utah? A study published five years ago seemed to suggest the answer was yes, at least for childhood leukemia (SN: 3/3/79, p. 133). But a report published this week by three National Cancer Institute (NCI) epidemiologists not only failed to confirm that earlier fallout-leukemia link, but also challenged the value of the statistical techniques from which the earlier study's conclusions were derived. Meanwhile, authors of the earlier study stand by their work and counter the NCI criticism with some of their own. Moreover they say follow-up studies they've conducted only strengthen their earlier contention that a fallout-leukemia risk is real. Clearly, the debate is far from over.

In 1979, Joseph Lyon and colleagues at the University of Utah College of Medicine in Salt Lake City reported an apparent excess in the number of deaths from childhood leukemia among children who had lived in southern Utah—a region that government records indicated would have received the highest fallout levels in the state.

Charles Land and colleagues at NCI in Bethesda, Md., recently attempted to verify the Utah team's findings using National Center for Health Statistics (NCHS) data. This necessitated changing the data base somewhat since Lyon's data went back to 1944, the NCHS data no earlier than 1950.

Lyon's team compared data for northern and southern Utah, since federal records indicated highest fallout exposures would have occurred in the southwest part of the state. In the pre-fallout years from 1944 to 1949, Utah records report that only three leukemias occurred in southern Utah, 38 in northern Utah.

It is largely about the significance and validity of this 1944-to-1949 data that the NCI and Utah teams are now arguing. According to Land, the 38 figure "is actually in keeping with the rest of the data [for subsequent years]. It's the 3, for a six-year period, that is unusual—in fact, it's a quarter as much as in northern Utah," based on the regions' respective population sizes.

Land says Lyon has taken the view that southern Utah's initially low leukemia rate was the norm for that area, and that the increase since 1950 is a result of the fallout. "But leukemia rates don't vary much by region, at least in developed countries," Land notes. And that observation, confirmed by NCI data, led Land's team to question whether the three leukemias for 1944 to 1949 might not result from misdiagnoses. An underreporting of leukemias would not be hard to imagine, the NCI researchers say, because of the historically low ratio of physicians to residents that has typified rural, southern Utah. The ratio of board-certified physicians per 100,000 residents remained more than 10 times higher in northern Utah than southern Utah through at least 1969, they point out.

Defense Nuclear Agency

Fallout in Utah from blasts at the Nevada Test Site, like this 1953 detonation, is being debated as a cause of leukemia.

But even if one accepts that three leukemias for the pre-1950 southern Utah cohort is accurate, Land said, when that rate is compared against leukemia rates for subsequent periods, no "significant" difference between northern and southern populations is found, despite the Lyon team's claim to the contrary. Writing in the Jan. 13 SCIENCE, Land and co-workers charge the Utah team with having used the wrong statistical technique to validate the significance of their findings. Land contends that Lyon "said he satisfied the criteria of statistical significance, but he hadn't. And to a statistician, to a scientist, that's a pretty severe mistake."

Lyon takes umbrage at this allegation. In an interview, he said, "I think there may be some areas of disagreement, but not fatal flaws." Lyon added that he stood behind the statistical methods and conclusions contained in his 1979 study.

Lyon also criticized the NCI researchers for grouping mortality figures in their study according to the age of the child at death instead of the calendar year in which the death occurred. Analyzing by calendar year, Lyon says, for 1959 to 1967 leukemia incidence roughly doubled across all age groups in southern Utah, relative to northern Utah. However, he adds, because leukemia tends to occur most often in children under the age of 4 years, less often in those 5 to 9, and relatively infrequently in children above 10, it's particularly significant that the 1959-to-1967 incidence figures report an eight-fold increase in leukemias for children 10 to 14 in southern Utah. Lyon says, "If you plot back who these folks are, they're the ones with the biggest cumulative exposure: They lived through all the bomb testing."

—*J. Raloff*

Voyager 2's outlook for Uranus

Early explorers setting out across the ocean did not know what they might find on the other side. A ring of fire? The edge of the world? The home of the gods? On Jan. 24, 1986, the Voyager 2 spacecraft will become the first probe from earth ever to visit a major planet that is invisible to the naked eyes of the people who launched the quest. Even the mere existence of distant Uranus, in fact, has been known for barely two centuries. To get there, Voyager 2 will have had to travel more than 3 billion miles and endure nearly eight and a half years in space.

It could be long years before such a foray is attempted again, so the engineers and scientists watching over the craft's welfare have more than even the usual reasons to keep close track of the health of their charge. Various problems have arisen during the flight, and there is the potential for others, but the Voyager team at the control center at Jet Propulsion Laboratory (JPL) in Pasadena, Calif., has found ways around some and devised procedures for dealing with others should they develop. Still, Uranus is the least-known world to which spacecraft have yet been sent, so interest is high.

The major area of concern is the craft's "scan platform," a movable, motor-driven mounting that carries its cameras, photopolarimeter and ultraviolet and infrared sensors. The platform worked fine through a 1979 encounter with Jupiter and exactly halfway through a 1981 rendezvous with Saturn. Just as Voyager 2 passed through the plane of Saturn's rings, however, the device was found to have become stuck in azimuth, one of its two axes of motion. A brief, early thought was that a particle from the rings (though they were thought to be well inside the crossing point) had jammed in the mechanism, but engineers later concluded that some lubricant had leaked out from between a drive gear and its spindle. Months of ground testing with identical systems, punctuated by a few gentle nudges of the actual platform suggest that at least slow movements might be possible, but if the device sticks solid during its close approach to Uranus, the result would be catastrophic.

An alternative would be not to use the scan platform at all, but instead to roll the whole spacecraft when motions in the azimuth direction were necessary. Some of Voyager 2's scientific instruments, mounted on the spacecraft itself rather than on the movable platform, are designed to operate in a known, fixed direction while other sensors move. Plasma-wave measurements, for example, important in studying the planet's ionosphere, radiation belts (if any) and interactions with the solar wind, require long periods of stable orientation. This could be a prob-

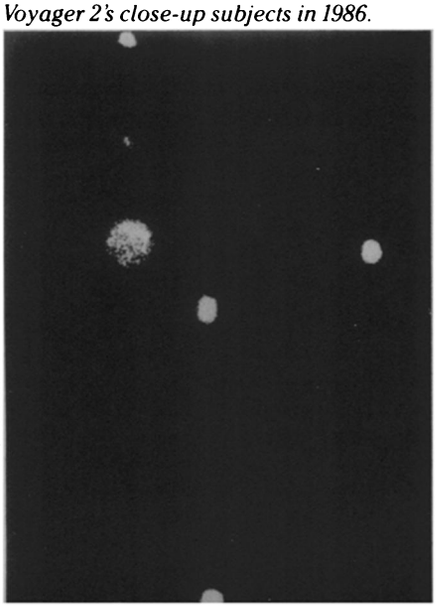
lem if Voyager 2's cameras are shifting around to photograph different parts of Uranus itself, its bizarre rings (known from earth primarily by their occasional blockage of the light from certain stars) and satellites. Adding to the problem is that the probe will be approaching Uranus at about 32,000 miles per hour (about one-third faster than its approach at Saturn and nearly twice that at Jupiter), so that it will be moving more quickly past its targets. In addition, the Uranian system is much smaller than those of the bigger planets, and the highly tilted orbits of its moons are nearly perpendicular to the oncoming spacecraft, instead of being laid out in a "flat" plane so that Voyager 2 would be flying across them. Both of these factors mean that the close-up measurements and photos will have to be compressed into a much shorter time, so that the flexibility of combining measurements from fixed and movable sensors would be welcome indeed.

In the last few months, fortunately, the Voyager engineers have devised a technique that they believe will let them use the scan platform after all, though perhaps only at its slowest turning rate (0.08° per second instead of 1° per second). Analysis and additional lab testing, expected to continue into September, has indicated that when the platform is about to jam, a pause will allow the lubricant to return to between the drive-gear and its shaft. And the engineers, says Charles Kohlhase of JPL, have found a way to see the jam coming. When the scan platform starts to get sticky, he says, the additional torque required is produced by longer electrical pulses in its azimuth drive motor. Under normal conditions, the pulses last about 100 milliseconds and provide more than adequate torque, but it is possible for commands to be radioed up from JPL to make the pulses so short that they are just barely long enough to let the platform move. At 6 msec, for example, it will move properly, but at 5 msec, says Kohlhase, it begins to drag a little. If the lubricant is starting to leak so that the friction of the system is increasing, however, it will take slightly longer pulses to overcome the drag—a warning of an impending jam.

The engineers thus plan to shorten the pulses for a few hours every few months as the spacecraft approaches Uranus, and then at lesser intervals as the time of the flyby nears. With the confidence inspired by this watch-dog technique, Voyager officials have decided to plan on using the scan platform after all—though there will be a set of commands ready for transmission at the touch of a button if it looks as though it will be necessary to switch to rolling the spacecraft.

Voyager 2 also has some other potential problem areas (SN: 2/6/82, p. 86), involving such aspects as the operating life of its narrow-angle camera, the fact that only one of its two receivers is working, and the loss of some small portions of its computer memory. But various remedies have been either planned or already implemented (except for the receiver, whose loss would cut Voyager off from further instructions from JPL), and none has deteriorated since the Saturn encounter. Expectations for the Uranus flyby are high, and if all goes well, Voyager 2 will head for Neptune in 1989. —*J. Eberhart*

Uranus (left, third from top) and its five known satellites—top to bottom: Umbriel, Miranda, Oberon, Ariel and Titania—photographed in infrared by William Sinton at Mauna Kea Observatory, Hawaii, will be Voyager 2's close-up subjects in 1986.



W. M. Sinton/Univ. of Hawaii

New biotech tool: Recombinant RNA

A novel laboratory method for producing large amounts of any selected RNA molecule has been announced by Columbia University scientists. They expect the technique to extend the already impressive power of biologists to analyze genes and cell processes and to produce proteins that are rare and valuable.

Previous work in gene splicing has employed methods to cut, recombine and reproduce molecules of DNA. Chemically DNA and RNA are distinguishable by only slight variations, but in cells they play very different roles. DNA is the archive of genetic information, whereas RNA implements the DNA-encoded instructions. In some viruses and in even smaller infectious agents, called viroids, RNA is the archival genetic material.

An RNA virus, Q beta (Qβ), provides the basis for the new technique. When it infects bacteria, its RNA acts as a template for Qβ replicase, which strings together RNA subunits. This enzyme rapidly produces many copies of the viral RNA, which get packaged to create a multitude of new Qβ viruses.

The trick behind the enzyme's proficiency is its exponential production of RNA molecules. Each RNA molecule produced can act as a template, along with the original Qβ RNA, for creating further RNA copies.

Although many researchers have tried to harness this enzyme's power, it was too specifically geared. In a cell the enzyme replicates only the Qβ viral RNA among thousands of bacterial RNA molecules. "The Qβ replicase needs to find its own template in a veritable universe of other RNAs," says Fred Russell Kramer of Columbia. The enzyme recognizes the Qβ RNA, and a few naturally occurring small RNAs (called variants) by a complex binding site in the center, and a specific region at the end also is necessary for replication.

Now Kramer, Donald Mills and Eleanor Miele report they have beguiled the enzyme to copy RNA of their choosing. They have developed two means of inserting selected RNA sequences into one of the small RNA variants that can serve as a template for Qβ replicase. The enzyme then replicates the insertion as well as the variant's sections.

In the first method, the scientists cut the variant at a point not crucial to its replication and add a selected piece of RNA, they report in the Dec. 15 JOURNAL OF MOLECULAR BIOLOGY. In more recent work they have constructed rings of DNA that encode the RNA of the variant. Then they can use the sophisticated recombinant DNA techniques to insert a gene or other stretch of DNA. This DNA ring can be converted to RNA and then immediately reproduced with the Qβ enzyme.

Three different RNA segments have been reproduced in quantity using these methods. "In a typical reaction 1 nanogram of RNA in one hour produces as much as 1 milligram of RNA, a million-fold amplification," Kramer says. "Size of the insert *per se* is not a problem, and the nature of the foreign sequence also seems not to be a problem." So far the largest insert, a segment from another virus, is 210 nucleotides (nucleic acid subunits), which is about the same size as the variant. "We haven't actually put in a 'monster' yet," Kramer says, "but there seems to be no reason why very large insertions can't be effective."

The Columbia scientists expect their technique to offer new opportunities for scientists to study, and to alter, the viruses and viroids that contain RNA as genetic information and to analyze the maturation of RNA in plant and animal cells. In addition, the recombinant RNA methods may allow scientists to make almost limitless amounts of RNA molecules that are unobtainable by current biotechnology methods, but that would allow laboratory production of yet more, commercially valuable biological products. —*J.A. Miller*