CHILDHOOD LEUKEMIA

Studies Set to Test Competing Theories About Early Infection

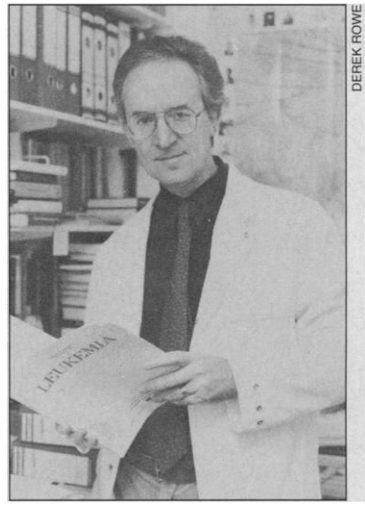
For fans of mystery stories, the literature on childhood leukemia makes fascinating reading. The prose may not have the punch of Raymond Chandler's, but all the elements of a detective novel are there, including obscure clues and false trails. Yet one thing is always missing—an ending. Leukemia, an uncontrolled proliferation of white blood cells, is the commonest form of cancer in young children. Yet only in a small minority of cases—including those that can be attributed to exposure to x-rays in utero or to birth defects—has anyone been able to put the clues together and find the cause of the disease.

"There has been an absolute dearth of new and exciting leads for the etiology of childhood leukemia," laments Leslie Robison, a cancer epidemiologist at the University of Minnesota. But that may be about to change. Setting the childhood leukemia research world abuzz are two British scientists—Melvyn Greaves, director of the Leukaemia Research Fund Centre at London's Institute for Cancer Research, and Leo Kinlen, director of Oxford University's Cancer Epidemiology Research Group—with a pair of related but different hypotheses that lay the blame on rare or unusual responses to childhood infections. Based on several epidemiological studies he has published in *The Lancet* and other journals over the past 4 years, Kinlen suspects that specific cancer-causing viruses are the culprits. But Greaves, writing in the journal *Leukemia* and speaking at numerous recent scientific meetings, has suggested that the immune response itself may bear much of the blame.

"These folks have at least put something on the table," says Robison. And Oxford University epidemiologist Sir Richard Doll says he finds the Greaves hypothesis "particularly exciting," although he believes that both ideas have merit. Two large-scale case-control studies of childhood cancer now under way have been designed in part to test these ideas: an NIH-funded study headed by Robison for the Children's Cancer Group in the United States, which will examine 2000 cases of acute lymphoblastic leukemia (ALL) over a 4-year period ending next 31 December; and a second in Great Britain, launched in March and led by a committee of British scientists chaired by Doll, which will cover 1000 ALL cases over the next 4 years.

For decades, leukemia sleuths have been sifting through a pile of confusing and inconsistent clues. Among them: much-publicized "clusters" of cases, such as those connected with the nuclear plant in Sellafield, England, and weak links to environmental factors, such as pesticides and electromagnetic radiation.

But a growing body of new evidence has led Greaves and Kinlen to conclude that the nature of a child's early exposure to viruses is the key to understanding childhood leukemia, although the two scientists differ in their views of exactly what role viruses are playing.



DEREK ROWE

Leukemia sleuth. Melvyn Greaves.

Greaves has taken particular note of the puzzling associations between a child's "lifestyle" and his risk of falling victim to leukemia. Unlike many other diseases, leukemia poses the greatest risk to children in developed countries: They are up to four times more likely to get the disease than those living in the developing world. And in the developed world, risks are higher for rich children. Last fall, a group of epidemiologists led by Gerald Draper of Oxford University's Childhood Cancer Research Group showed that childhood leukemia incidence in the wealthiest one-fifth of the British population was 10% to 15% higher than in the poorest one-fifth.

Although Greaves does not rule out Kinlen's suspicion that a specific leukemia virus, analogous to HTLV-1 in some adult human T cell leukemias, may be the villain, he believes that viruses may be playing a more indirect role. Focusing on the most common subtype of childhood leukemia, common acute lymphoblastic leukemia, Greaves postulates that the disease is caused by at least two spontaneous mutations. The first occurs in utero, when the fetus's immature B cells are rapidly dividing, a situation in which copying errors might cause high mutation rates.

Stress response. Then Greaves makes the novel proposal that a second mutation occurs later in childhood when the same B cells again divide rapidly—this time as a result of exposure to common viruses. The level of such "proliferative stress," says Greaves, could be higher in children exposed to viruses somewhat later in life, when their more developed immune systems are capable of a stronger immune response. In contrast, children exposed to diseases early on will already have developed limited immunity and their immune systems will not be under the same stress. Greaves also envisages other ways that viruses could induce proliferation of B cells other than direct stimulation of the immune system, for example by infecting the bone marrow where they are produced.

"I find the Greaves hypothesis biologically very attractive," says Doll. "It provides an explanation for the increase in childhood leukemia that occurred between about 1920 and 1945 in Britain, and a bit later in the United States," a period when the standards of health and hygiene dramatically improved, which meant that newborn babies and young children were exposed to fewer infectious agents. And Draper adds that the hypothesis "fits in very well with the social class effect," because the offspring of wealthier families may lead more sheltered lives and be exposed to diseases later in childhood.

But not everyone is jumping aboard the Greaves bandwagon. "There is no precedent for his idea, and that is an important weakness," says Kinlen. "It's more likely that we have a specific infection here than a completely new process of disease causation."

Kinlen focuses on his own studies, the most dramatic of which concerns the "New Towns" built in postwar Britain to relieve overcrowding in large cities. Kinlen found that in rural New Towns, leukemia rates were up to six times greater than expected. He argues that these results can be explained if leukemia is directly caused by one or more specific viruses. "When many people come together from different geographic regions," he says, "an increase of contacts must occur between infected and susceptible individuals—the basis for the spread of any infection." Even if only a small proportion of children exposed to leukemia viruses contract the disease, a measurable increase could occur.

No one expects the case control studies now under way to provide a definitive solution to the mystery of childhood leukemia. But they might provide some important new leads. "If we could identify a culprit virus," says Greaves, "then obviously the opportunity for vaccination and prevention presents itself." But if it is the timing of exposure to common viruses that is key, he adds, "one possible implication is that we are being overly hygienic." Childhood leukemia, says Greaves, may be a paradoxical price of progress.

–Michael Balter

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