Childhood cancer

Germ theory

It may be possible to prevent childhood leukaemia by exposing children to more microbes

The long struggle to cure acute lymphoblastic leukaemia (ALL), a childhood blood cancer, is a stand-out tale in the history of medicine. It was a massive endeavour, over decades, with many toxic drugs being tested in different combinations on dying children. It succeeded in the end. Half a century ago, survival rates were less than 0.1%. Today they are about 90%. Yet the cure brings unpleasant side effects, including problems with memory and concentration, and sometimes even other cancers. Globally, rates of ALL seem to be rising by about 1% a year. Yet it is almost non-existent in the poorest countries.

Its causes remain unclear and even controversial. A charity called Children with Cancer UK, for instance, still suggests the disease is connected to electromagnetic radiation from power lines. Into this debate comes Mel Greaves, of the Institute of Cancer Research in London. In a paper in Nature Reviews Cancer, Dr Greaves has marshalled decades of research into ALL alongside some new lab work, and created a comprehensive theory about its origins.

His theory involves three steps. First is a genetic mutation. Then there is an infectious illness. Lastly, the child’s immune system reacts badly to that infection. And this chain of events is more likely in those who had little exposure to germs and bacteria in early childhood.

The first part of Dr Greaves’s theory dates back to 1988. Studies on twins showed that, where both suffered from ALL, the cause could often be traced back to a mutation in just one. Specifically, if they had shared a placenta, then genetic errors in the bone marrow, where blood cells are made, would result in one twin producing mutant cells. Those cells could then spread through the placenta into the other twin, even if his genes were free from the error. Such mutant cells are necessary, but not sufficient, for the later development of ALL.

Bugs are a feature

Lab work by Dr Greaves suggests that the genetic error that produces these pre-leukaemia cells is much more common than ALL itself. When he screened blood from umbilical cords in British hospitals, he found that six babies among 567 had pre-leukaemia cells. But the disease occurs in just in 2,000 British children.

This is where the second and third steps of the theory come in. For those pre-leukaemia cells to develop into a full-blown blood cancer, a child has to be exposed to an infectious disease, and his immune system must then overreact to the threat. And there is substantial, albeit circumstantial, evidence to suggest that the risk of such an overreaction is raised by a lack of exposure to infections and microbes in the first year of a child’s life.

In the 1990s the UK Children’s Cancer Study Group found that babies who had been sent to child care in the first year of their lives were less likely to develop childhood leukaemia. That finding has since been replicated around the world. It is bolstered by a separate and fairly well-established inverse relationship between common diseases in early life and the risk of developing ALL.

More suggestive evidence comes from the fact that childhood leukaemia rates are higher in children born by Caesarean section, which avoids exposing them to microbes in the vagina. Dr Greaves’s theory also offers an explanation for rare but puzzling geographical clusters of ALL. An infection might sweep through a community and pick out the children who are overreactive carriers of pre-leukaemia cells.

In Milan in 2009, for instance, seven children developed ALL in rapid succession. All had been infected with swine flu three to six months before. None had been to nursery before the age of one. There is no reason to think that one infection is more likely than another to trigger ALL. But flu is common enough that researchers have been able to detect an uptick of ALL a few months after the virus sweeps through a country. Work in mice has proved that early stimulation of their immune systems protects against a murine version of ALL.

That is the evidence. So far, though, the precise mechanism remains mysterious. One candidate is a type of inflammatory molecule known as a cytokine—specifically, one called transforming growth factor-β, which seems to selectively boost the growth of pre-leukaemia cells. It is also known to promote other cancers.

Breastfeeding, which helps to calibrate a baby’s immune system, can help. But if Dr Greaves is right, then another message for parents is to encourage early social contact.
tact with other infants, which encourages the swapping of germs.

Dr Greaves is not the first to have such ideas. The theory that modern humans are under-exposed to micro-organisms and parasites is known as the “hygiene hypothesis”. It has been invoked as an explanation for rising rates in the rich world of autoimmune disorders such as type-1 diabetes, multiple sclerosis and allergies. And ALL may not be the only cancer implicated. A malfunctioning immune system can cause chronic inflammation. That has been suggested as a risk factor in the development of oesophageal cancer, colon cancer and some cancers of the pancreas.

The hygiene hypothesis is a striking idea. But it is not yet proved. And even if it were, balancing the risks could be tricky, says Donna Lancaster, a paediatric oncologist at the Royal Marsden NHS Foundation Trust in London. Hygiene has benefits as well as drawbacks. Exposing children to germs means that many will become ill, and a few will become seriously so. One idea for squaring the circle—albeit a very speculative one—is a carefully designed vaccine that gives just the right nudge to an infant’s immune system without the risk of making them properly ill.

If Dr Greaves’s theory stands the test of time then the reputation of the hygiene hypothesis will rise. It even offers a possible explanation for the statistical link between power lines and leukaemia. Parents who fret about their children playing near power lines might keep them indoors—away from dirt, germs and each other.