THE BRAIN, INTERRUPTED

Babies are increasingly surviving premature birth — but researchers are only beginning to understand the lasting consequences for their mental development.

BY ALISON ABBOTT

Fabienne never found out why she went into labour three months too early. But on a quiet afternoon in June 2007, she was hit by accelerating contractions and was rushed to the nearest hospital in rural Switzerland, near Lausanne. When her son, Hugo, was born at 26 weeks of gestation rather than the typical 40, he weighed just 950 grams and was immediately placed in intensive care. Three days later, doctors told Fabienne that ultrasound pictures of Hugo's brain indicated that he had had a severe haemorrhage from his immature blood vessels. "I just exploded into tears," she says.

Both she and her husband understood that the prognosis for Hugo was grim: he had a very high risk of cerebral palsy, a neurological condition that can lead to a life of severe disability. The couple agreed that they did not want to subject their child to that. "We immediately told the doctors that we did not want fierce medical intervention to keep him alive — and saw the relief on the doctors' faces," recalls Fabienne, who requested that her surname not be used. That night was the most tortured of her life.

The next day, however, before any change had been made to Hugo's treatment, his doctors proposed a new option to confirm the diagnosis: a brain scan using magnetic resonance imaging (MRI). This technique, which had been newly adapted for premature babies, would allow the doctors to predict the risk of cerebral palsy more accurately than with ultrasound alone, which has a high false-positive rate. Hugo's MRI scan showed that the damage caused by the brain haemorrhage was limited,

ILLUSTRATION: PADDY MILLS

and his risk of severe cerebral palsy was likely to be relatively low. So just 24 hours after their decision to let his life end, Hugo's parents did an about-turn. They agreed that the doctors should try to save him.

Thanks to medical advances since the 1970s, premature infants — those born before 37 weeks of gestation — are increasingly able to survive. Some hospitals now try to save babies born as early as 22 weeks. But those developments are forcing doctors and parents to grapple with difficult decisions, because the chances of severe disability increase with the extent of prematurity. Cerebral palsy, for example, affects 1–2% of babies born at term, 9% of those born earlier than 32 weeks and 18% of those born at 26 weeks.

That is just half the story. Neuroscientists are developing an increasingly sophisticated picture of premature infants' brains that could help to inform medical decisions and treatments. From some long-term studies, they are learning that premature children face a higher risk than was previously thought of developing cognitive or behavioural problems — according to some studies, as many as half of them will.

Researchers are starting to ask why this should be, whether it could be avoided and what is the best way to provide educational support for the affected children. "We need to gather a lot more data to understand what the best strategies are," says Petra Hüppi, a neonatologist and developmental paediatrician at the University of Geneva in Switzerland, who is following the brain development of children who were born prematurely.

EARLY BIRTHDAY

Prematurity — also called pre-term birth — is extremely common. According to World Health Organization statistics from 2012, more than one in 10 babies — around 15 million in total — are born prematurely each year. The great majority are born between 32 and 37 weeks of gestation, but 1.6 million are born between 28 and 32 weeks and 780,000 are born 'extremely pre-term', before 28 weeks (see 'Born too soon').

In low-income countries, more than 90% of extremely pre-term babies born alive soon die, which helps to explain why prematurity is now the second biggest cause of death in children under five, after pneumonia. But in richer countries, with sophisticated neonatal intensive-care facilities, more than 90% of these extremely pre-term babies survive, and doctors are continuing to push the age of survival even earlier in development. Doctors in the United States are debating a controversial recommendation to lower the gestational age at which a baby should be considered potentially viable from 24 weeks to 23 weeks. In Japan, babies born at 22 weeks have been considered viable since 1991.

Parents of premature children face agonizing waits as their children fight for their lives. Hugo's parents endured tense weeks during which their son had a series of operations to fix damaged organs, and to create essential connections between major blood vessels that had not had time to develop before birth. They knew he could still die at any time. "But I felt like we were back on the TGV," says Fabienne, referring to the French high-speed trains. "The train goes fast and it rocks frighteningly — but we were on it again."

But what happens after the immediate danger has passed? Just a few studies have so far followed up the long-term fate of premature babies, because it is time-consuming and expensive to track them with sophisticated cognitive and behavioural tests over many years.

> "We were shocked to see just how many children had problems."

One of the first studies to show the extent of developmental problems was EPIPAGE, which looked at a cohort of all live births between 22 and 32 weeks of gestation from 9 regions of France in 1997, and a reference group of 664 full-term babies[1]. Up to half of the premature babies who survived to five years of age had some sort of neurodevelopmental problem by then, and the impairments in cognitive development grew more pronounced for each extra week of prematurity. On a score of cognitive ability, the team observed impairment in 44% of those born between 24 and 25 weeks of gestation and 26% of those born at 32 weeks, compared with 12% of full-term controls.

"We were shocked to see just how many children had problems," says Hüppi. Moderately premature babies may be at lower risk than extremely premature babies, she notes, but there are many more of them.

The effects seem to continue into adulthood. Developmental psychologist Dieter Wolke led an unusual study of hundreds of children born between 26 and 31 weeks of gestation in Bavaria in the mid-1980s. He assessed them at six years old[2], and again at 26 years[3]. Last year, he reported[3] that most of those who had cognitive problems as children still had them as adults: one-quarter of them had moderate to severe cognitive deficits, and half had mild cognitive deficits. Most of those who experienced problems had short attention spans, and as a group they tended to underachieve academically and career-wise.

Wolke, who is currently at the University of Warwick, UK, observed subtler lifestyle differences, too. "They are less likely to take risks, smoke, drink or have early sexual relationships," he says.

Scientists are still struggling to understand the physical changes in the brain that underlie all these differences. The brain is made up of grey matter, which comprises densely packed cell bodies, and white matter, the long-reach axons of cells that connect different brain regions. These axons are covered in a protective coating called myelin during development, in a precise sequence that begins in the womb and continues for the first decade or so after birth.

In the premature brain, immature, fragile blood vessels struggle to provide tissue with enough oxygen for normal development. When a vessel ruptures, crucial areas of white matter are destroyed and cerebral palsy can result. But very little is known about what causes the more subtle brain problems that cohort studies of premature infants are revealing.

TOO MUCH TOO SOON

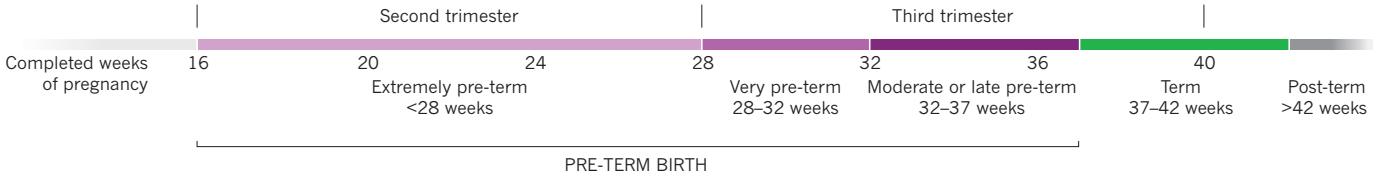
Scientists suspect that when the brain is forced to carry out a crucial part of its development while the child is in the outside world instead of a warm, watery womb, it receives inappropriate signals from the environment that affect how its neurons are linked into networks. "The premature brain gets subjected to quite different sensory inputs — like visual stimulation and gravity effects — which it is not supposed to be subject to," says Ghislaine Dehaene-Lambertz of the INSERM-CEA Cognitive Neuroimaging Unit in Paris, who studies language development in infants. "They can be sudden, intense but also unpredictable." Some of these unnatural sensory signals are inevitably provided by the intensive medical procedures that keep premature babies alive.

Pioneering brain-scanning studies support the idea that altered networks play a part in cognitive problems. Hüppi's Swiss collaboration looked at 52 six-year-olds who had been born prematurely, using MRI scans optimized to reveal tracts of neurons connecting brain regions[4]. Compared with children born at term, the premature children's neuronal tracts were organized less efficiently, often taking a more meandering path. These changes in organization were correlated with reduced social and cognitive skills.

In another study, neonatologist Jeffrey Neil, then at St. Louis Children's Hospital in Missouri, and his team used functional MRI to study the premature brain at rest. The low-level, idling activity of a resting brain gives a read-out of its working connections, whose general topology is laid out before birth (see *Nature* **489,** 356–358; 2012). The team showed[5] that in babies born between 23 and 29 weeks of gestation, this 'resting-state connectivity' tends on average to be less complex and active at term-equivalent age than it is in full-term babies at birth. Another study — on the 26-year-old Bavarians — showed[6] that this

BORN TOO SOON

Just over 11% of live births worldwide are pre-term — before 37 weeks of gestation — and premature birth is the second largest cause of child deaths in under-fives. The medical risks increase with the extent of prematurity; neuroscientists now think that some effects on brain development may last into adulthood.



SOURCE: H. BLENCOWE *ET AL. LANCET* **379,** 2162–2172 (2012)

22 WEEKS
Some hospitals now try to save babies born as early as 22 weeks.

22–32 WEEKS
One long-term study found that up to half of children born in this window have some neurodevelopmental problem at age five.

23–39 WEEKS
Brain-scanning studies point to atypical structural and functional connections in the brains of premature infants.

24 WEEKS
50% chance of survival with neonatal intensive care in most high-income countries.

26 WEEKS
Cerebral palsy affects around 10% of very pre-term babies, but 18% of those born at 26 weeks.

34 WEEKS
50% chance of survival with neonatal intensive care in many low-income countries.

reduced complexity of resting-state connectivity stretches into adulthood.

Researchers agree that the most revealing studies would monitor the brains of premature babies and full-term comparison babies from as early as possible after birth, with follow-up scans and assessments throughout life. But such studies are difficult, and not only because it is hard to keep tabs on families who may move house, lose interest or lose touch over the years. Parents are rarely keen for their newborns — whether premature or full-term — to be whisked away into the loud and lonely chamber of a distant MRI machine without a burning medical reason. (In some countries, such as the Netherlands, it is illegal to do so.) And not all obstetricians are comfortable with subjecting delicate premature babies to brain scans at a medically and emotionally fraught time. Fabienne was happy for Hugo to be scanned, but recalls how painfully long it took to get from the paediatric ward to the scanning suite in her hospital. "I felt half-dazed walking alongside Hugo in his incubator through a long underground tunnel to get there," she says. "It looked like the tunnel you are supposed to see when you are dying."

A small vanguard of scientists and clinicians is pushing ahead, and several large long-term studies are under way around the world, collecting neurological, cognitive, behavioural and genetic data from birth, along with brain scans.

In France, EPIPAGE 2 is now running, and has recruited more than 4,200 premature babies from all over the country[7]. In the United Kingdom, a team led by neonatologist David Edwards of King's College London has launched a study that will track children from their time *in utero* until they are two years old, collecting brain scans and blood samples along the way. Some of these children will inevitably be born prematurely, and the plan is to identify molecular signatures that might predict which of those infants are particularly vulnerable, or resistant, to altered neurodevelopment.

Edwards' preliminary studies[8] on premature babies suggest that some genes — including several associated with lipid metabolism, which is crucial for white-matter development — may modify the risk of altered brain development. "Having a particular genetic profile might make certain babies less vulnerable," he says.

BRAIN PROTECTION

With scientists still working to identify the molecular, cellular and network differences in the premature brain, finding treatments seems a fond hope. But Hüppi is attempting to do it. She is conducting a clinical study of erythropoietin, or EPO, a drug that stimulates the production of red blood cells. It is already a standard treatment to aid oxygenation of internal organs — not to mention being a favourite among endurance-sport cheats — and it is also thought to protect and support neurons.

Anecdotal reports had suggested that erythropoietin might help long-term neurodevelopment, and Hüppi's team is assessing this in a prospective, randomized and controlled study in nearly 500 very premature babies born in Switzerland, who are being MRI scanned at term-equivalent age. The first results, published in 2014, showed[9] that treated babies had fewer signs of neurological problems than did children in a control group. But the acid test, says Hüppi, will come when they are assessed at two years old, when neurodevelopment has proceeded further.

Where does all this leave parents, who still have to make decisions about their children's treatment with only limited information about the long-term prognosis? Some, such as Fabienne, can be helped by MRI scans that can detect damage in white and grey matter, and make it possible to predict the risk of severe brain damage more precisely than in the past. Hüppi says that the technology helps doctors to advise parents, "and it is a terrible responsibility if we are wrong". But this does little to identify which children will have milder developmental problems, or what those might be.

Edwards and others think that brain imaging alone can never provide that type of information — but that combining scans with genetic and other molecular and clinical data may eventually lead to much greater precision. Should this become possible, it will throw open a whole new debate about how best to ameliorate any future problems for premature children, through very specific social and educational support — something that neuroscientists and education experts are only beginning to grapple with.

Fabienne, like many parents of premature children, would like to have that information. Hugo, who is now seven, occupies most of her time. He has difficulties with fine movements, and some visual problems; he also needs a lot of extra assistance at school. Fabienne is deeply engaged with educational training programmes, which she hopes will be helpful, although she cannot know for sure. But Hugo is an unadulterated joy to her, and she is endlessly grateful for the MRI scans that were so crucial in the decision to save him. "Neuroscience was able to say that Hugo would be able to have a reasonable quality of life," she says.

And she monitors from a distance the new wave of scientific interest in the brains of premature babies. "Neuroscience is coming up with a lot of good information — I really hope that they will soon translate what they are discovering into concrete actions that parents can usefully undertake." ■

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