FERTILE MINDS

FROM BIRTH, A BABY'S BRAIN CELLS PROLIFERATE WILDLY, MAKING CONNECTIONS THAT MAY SHAPE A LIFETIME OF EXPERIENCE. THE FIRST THREE YEARS ARE CRITICAL

By J. MADELEINE NASH

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Rat-a-tat-tat. rat-a-tat-tat. Rat-a-tat-tat. If scientists could eavesdrop on the brain of a human embryo 10, maybe 12 weeks after conception, they would hear an astonishing racket. Inside the womb, long before light first strikes the retina of the eye or the earliest dreamy images flicker through the cortex, nerve cells in the developing brain crackle with purposeful activity. Like teenagers with telephones, cells in one neighborhood of the brain are calling friends in another, and these cells are calling their friends, and they keep calling one another over and over again, " almost," says neurobiologist Carla Shatz of the University of California, Berkeley, "as if they were autodialing."

But these neurons--as the long, wiry cells that carry electrical messages through the nervous system and the brain are called--are not transmitting signals in scattershot fashion. That would produce a featureless static, the sort of noise picked up by a radio tuned between stations. On the contrary, evidence is growing that the staccato bursts of electricity that form those distinctive rat-a-tat-tats arise from coordinated waves of neural activity, and that those pulsing waves, like currents shifting sand on the ocean floor, actually change the shape of the brain, carving mental circuits into patterns that over time will enable the newborn infant to perceive a father's voice, a mother's touch, a shiny mobile twirling over the crib.

Of all the discoveries that have poured out of neuroscience labs in recent years, the finding that the electrical activity of brain cells changes the physical structure of the brain is perhaps the most breathtaking. For the rhythmic firing of neurons is no longer assumed to be a by-product of building the brain but essential to the process, and it begins, scientists have established, well before birth. A brain is not a computer. Nature does not cobble it together, then turn it on. No, the brain begins working long before it is finished. And the same processes that wire the brain before birth, neuroscientists are finding, also drive the explosion of learning that occurs immediately afterward.

At birth a baby's brain contains 100 billion neurons, roughly as many nerve cells as there are stars in the Milky Way. Also in place are a trillion glial cells, named after the Greek word for glue, which form a kind of honeycomb that protects and nourishes the neurons. But while the brain contains virtually all the nerve cells it will ever have, the pattern of wiring between them has yet to stabilize. Up to this point, says Shatz, "what the brain has done is lay out circuits that are its best guess about what's required for vision, for language, for whatever." And now it is up to neural activity--no longer spontaneous, but driven by a flood of sensory experiences--to take this rough blueprint and progressively refine it.

During the first years of life, the brain undergoes a series of extraordinary changes. Starting shortly after birth, a baby's brain, in a display of biological exuberance, produces trillions more connections between neurons than it can possibly use. Then, through a process that resembles Darwinian competition, the brain eliminates connections, or synapses, that are seldom or never used. The excess synapses in a child's brain undergo a draconian pruning, starting around the age of 10 or earlier, leaving behind a mind whose patterns of emotion and thought are, for better or worse, unique.

Deprived of a stimulating environment, a child's brain suffers. Researchers at Baylor College of Medicine, for example, have found that children who don't play much or are rarely touched develop brains 20% to 30% smaller than normal for their age. Laboratory animals provide another provocative parallel. Not only do young rats reared in toy-strewn cages exhibit more complex behavior than rats confined to sterile, uninteresting boxes, researchers at the University of Illinois at Urbana-Champaign have found, but the brains of these rats contain as many as 25% more synapses per neuron. Rich experiences, in other words, really do produce rich brains.

The new insights into brain development are more than just interesting science. They have profound implications for parents and policymakers. In an age when mothers and fathers are increasingly pressed for time--and may already be feeling guilty about how many hours they spend away from their children--the results coming out of the labs are likely to increase concerns about leaving very young children in the care of others. For the data underscore the importance of hands-on parenting, of finding the time to cuddle a baby, talk with a toddler and provide infants with stimulating experiences.

The new insights have begun to infuse new passion into the political debate over early education and day care. There is an urgent need, say child-development experts, for preschool programs designed to boost the brain power of youngsters born into impoverished rural and inner-city households. Without such programs, they warn, the current drive to curtail welfare costs by pushing mothers with infants and toddlers into the work force may well backfire. "There is a time scale to brain development, and the most important year is the first," notes Frank Newman, president of the Education Commission of the States. By the age of three, a child who is neglected or abused bears marks that, if not indelible, are exceedingly difficult to erase.

But the new research offers hope as well. Scientists have found that the brain during the first years of life is so malleable that very young children who suffer strokes or injuries that wipe out an entire hemisphere can still mature into highly functional adults. Moreover, it is becoming increasingly clear that well-designed preschool programs can help many children overcome glaring deficits in their home environment. With appropriate therapy, say researchers, even serious disorders like dyslexia may be treatable. While inherited problems may place certain children at greater risk than others, says Dr. Harry Chugani, a pediatric neurologist at Wayne State University in Detroit, that is no excuse for ignoring the environment's power to remodel the brain. "We may not do much to change what happens before birth, but we can change what happens after a baby is born," he observes.

Strong evidence that activity changes the brain began accumulating in the 1970s. But only recently have researchers had tools powerful enough to reveal the precise mechanisms by which those changes are brought about. Neural activity triggers a biochemical cascade that reaches all the way to the nucleus of cells and the coils of DNA that encode specific genes. In fact, two of the genes affected by neural activity in embryonic fruit flies, neurobiologist Corey Goodman and his colleagues at Berkeley reported late last year, are identical to those that other studies have linked to learning and memory. How thrilling, exclaims Goodman, how intellectually satisfying that the snippets of DNA that embryos use to build their brains are the very same ones that will later allow adult organisms to process and store new information.

As researchers explore the once hidden links between brain activity and brain structure, they are beginning to construct a sturdy bridge over the chasm that previously separated genes from the environment. Experts now agree that a baby does not come into the world as a genetically preprogrammed automaton or a blank slate at the mercy of the environment, but arrives as something much more interesting. For this reason the debate that engaged countless generations of philosophers--whether nature or nurture calls the shots--no longer interests most scientists. They are much too busy chronicling the myriad ways in which genes and the environment interact. "It's not a competition," says Dr. Stanley Greenspan, a psychiatrist at George Washington University. "It's a dance."

THE IMPORTANCE OF GENES

That dance begins at around the third week of gestation, when a thin layer of cells in the developing embryo performs an origami-like trick, folding inward to give rise to a fluid-filled cylinder known as the neural tube. As cells in the neural tube proliferate at the astonishing rate of 250,000 a minute, the brain and spinal cord assemble themselves in a series of tightly choreographed steps. Nature is the dominant partner during this phase of development, but nurture plays a vital supportive role. Changes in the environment of the womb--whether caused by maternal malnutrition, drug abuse or a viral infection--can wreck the clockwork precision of the neural assembly line. Some forms of epilepsy, mental retardation, autism and schizophrenia appear to be the results of developmental processes gone awry.

But what awes scientists who study the brain, what still stuns them, is not that things occasionally go wrong in the developing brain but that so much of the time they go right. This is all the more remarkable, says Berkeley's Shatz, as the central nervous system of an embryo is not a miniature of the adult system but more like a tadpole that gives rise to a frog. Among other things, the cells produced in the neural tube must migrate to distant locations and accurately lay down the connections that link one part of the brain to another. In addition, the embryonic brain must construct a variety of temporary structures, including the neural tube, that will, like a tadpole's tail, eventually disappear.

What biochemical magic underlies this incredible metamorphosis? The instructions programmed into the genes, of course. Scientists have recently discovered, for instance, that a gene nicknamed "sonic hedgehog" (after the popular video game Sonic the Hedgehog) determines the fate of neurons in the spinal cord and the brain. Like a strong scent carried by the wind, the protein encoded by the hedgehog gene (so called because in its absence, fruit-fly embryos sprout a coat of prickles) diffuses outward from the cells that produce it, becoming fainter and fainter. Columbia University neurobiologist Thomas Jessell has found that it takes middling concentrations of this potent morphing factor to produce a motor neuron and lower concentrations to make an interneuron (a cell that relays signals to other neurons, instead of to muscle fibers, as motor neurons do).

Scientists are also beginning to identify some of the genes that guide neurons in their long migrations. Consider the problem faced by neurons destined to become part of the cerebral cortex. Because they arise relatively late in the development of the mammalian brain, billions of these cells must push and shove their way through dense colonies established by earlier migrants. "It's as if the entire population of the East Coast decided to move en masse to the West Coast," marvels Yale University neuroscientist Dr. Pasko Rakic, and marched through Cleveland, Chicago and Denver to get there.

But of all the problems the growing nervous system must solve, the most daunting is posed by the wiring itself. After birth, when the number of connections explodes, each of the brain's billions of neurons will forge links to thousands of others. First they must spin out a web of wirelike fibers known as axons (which transmit signals) and dendrites (which receive them). The objective is to form a synapse, the gap-like structure over which the axon of one neuron beams a signal to the dendrites of another. Before this can happen, axons and dendrites must almost touch. And while the short, bushy dendrites don't have to travel very far, axons--the heavy-duty cables of the nervous system--must traverse distances that are the microscopic equivalent of miles.

What guides an axon on its incredible voyage is a "growth cone," a creepy, crawly sprout that looks something like an amoeba. Scientists have known about growth cones since the turn of the century. What they didn't know until recently was that growth cones come equipped with the molecular equivalent of sonar and radar. Just as instruments in a submarine or airplane scan the environment for signals, so molecules arrayed on the surface of growth cones search their surroundings for the presence of certain proteins. Some of these proteins, it turns out, are attractants that pull the growth cones toward them, while others are repellents that push them away.

THE FIRST STIRRINGS

Up to this point, genes have controlled the unfolding of the brain. As soon as axons make their first connections, however, the nerves begin to fire, and what they do starts to matter more and more. In essence, say scientists, the developing nervous system has strung the equivalent of telephone trunk lines between the right neighborhoods in the right cities. Now it has to sort out which wires belong to which house, a problem that cannot be solved by genes alone for reasons that boil down to simple arithmetic. Eventually, Berkeley's Goodman estimates, a human brain must forge quadrillions of connections. But there are only 100,000 genes in human DNA. Even though half these genes--some 50,000--appear to be dedicated to constructing and maintaining the nervous system, he observes, that's not enough to specify more than a tiny fraction of the connections required by a fully functioning brain.

In adult mammals, for example, the axons that connect the brain's visual system arrange themselves in striking layers and columns that reflect the division between the left eye and the right. But these axons start out as scrambled as a bowl of spaghetti, according to Michael Stryker, chairman of the physiology department at the University of California at San Francisco. What sorts out the mess, scientists have established, is neural activity. In a series of experiments viewed as classics by scientists in the field, Berkeley's Shatz chemically blocked neural activity in embryonic cats. The result? The axons that connect neurons in the retina of the eye to the brain never formed the left eye-right eye geometry needed to support vision.

But no recent finding has intrigued researchers more than the results reported in October by Corey Goodman and his Berkeley colleagues. In studying a deceptively simple problem--how axons from motor neurons in the fly's central nerve cord establish connections with muscle cells in its limbs--the Berkeley researchers made an unexpected discovery. They knew there was a gene that keeps bundles of axons together as they race toward their muscle-cell targets. What they discovered was that the electrical activity produced by neurons inhibited this gene, dramatically increasing the number of connections the axons made. Even more intriguing, the signals amplified the activity of a second gene--a gene called CREB.

The discovery of the CREB amplifier, more than any other, links the developmental processes that occur before birth to those that continue long after. For the twin processes of memory and learning in adult animals, Columbia University neurophysiologist Eric Kandel has shown, rely on the CREB molecule. When Kandel blocked the activity of CREB in giant snails, their brains changed in ways that suggested that they could still learn but could remember what they learned for only a short period of time. Without CREB, it seems, snails--and by extension, more developed animals like humans--can form no long-term memories. And without long-term memories, it is hard to imagine that infant brains could ever master more than rudimentary skills. "Nurture is important," says Kandel. "But nurture works through nature."

EXPERIENCE KICKS IN

When a baby is born, it can see and hear and smell and respond to touch, but only dimly. The brain stem, a primitive region that controls vital functions like heartbeat and breathing, has completed its wiring. Elsewhere the connections between neurons are wispy and weak. But over the first few months of life, the brain's higher centers explode with new synapses. And as dendrites and axons swell with buds and branches like trees in spring, metabolism soars. By the age of two, a child's brain contains twice as many synapses and consumes twice as much energy as the brain of a normal adult.

University of Chicago pediatric neurologist Dr. Peter Huttenlocher has chronicled this extraordinary epoch in brain development by autopsying the brains of infants and young children who have died unexpectedly. The number of synapses in one layer of the visual cortex, Huttenlocher reports, rises from around 2,500 per neuron at birth to as many as 18,000 about six months later. Other regions of the cortex score similarly spectacular increases but on slightly different schedules. And while these microscopic connections between nerve fibers continue to form throughout life, they reach their highest average densities (15,000 synapses per neuron) at around the age of two and remain at that level until the age of 10 or 11.

This profusion of connections lends the growing brain exceptional flexibility and resilience. Consider the case of 13-year-old Brandi Binder, who developed such severe epilepsy that surgeons at UCLA had to remove the entire right side of her cortex when she was six. Binder lost virtually all the control she had established over muscles on the left side of her body, the side controlled by the right side of the brain. Yet today, after years of therapy ranging from leg lifts to math and music drills, Binder is an A student at the Holmes Middle School in Colorado Springs, Colorado. She loves music, math and art--skills usually associated with the right half of the brain. And while Binder's recuperation is not 100%--for example, she has never regained the use of her left arm--it comes close. Says UCLA pediatric neurologist Dr. Donald Shields: "If there's a way to compensate, the developing brain will find it."

What wires a child's brain, say neuroscientists--or rewires it after physical trauma--is repeated experience. Each time a baby tries to touch a tantalizing object or gazes intently at a face or listens to a lullaby, tiny bursts of electricity shoot through the brain, knitting neurons into circuits as well defined as those etched onto silicon chips. The results are those behavioral mileposts that never cease to delight and awe parents. Around the age of two months, for example, the motor-control centers of the brain develop to the point that infants can suddenly reach out and grab a nearby object. Around the age of four months, the cortex begins to refine the connections needed for depth perception and binocular vision. And around the age of 12 months, the speech centers of the brain are poised to produce what is perhaps the most magical moment of childhood: the first word that marks the flowering of language.

When the brain does not receive the right information--or shuts it out--the result can be devastating. Some children who display early signs of autism, for example, retreat from the world because they are hypersensitive to sensory stimulation, others because their senses are underactive and provide them with too little information. To be effective, then, says George Washington University's Greenspan, treatment must target the underlying condition, protecting some children from disorienting noises and lights, providing others with attention-grabbing stimulation. But when parents and therapists collaborate in an intensive effort to reach these abnormal brains, writes Greenspan in a new book, The Growth of the Mind (Addison-Wesley, 1997), three-year-olds who begin the descent into the autistic's limited universe can sometimes be snatched back.

Indeed, parents are the brain's first and most important teachers. Among other things, they appear to help babies learn by adopting the rhythmic, high-pitched speaking style known as Parentese. When speaking to babies, Stanford University psychologist Anne Fernald has found, mothers and fathers from many cultures change their speech patterns in the same peculiar ways. "They put their faces very close to the child," she reports. "They use shorter utterances, and they speak in an unusually melodious fashion." The heart rate of infants increases while listening to Parentese, even Parentese delivered in a foreign language. Moreover, Fernald says, Parentese appears to hasten the process of connecting words to the objects they denote. Twelve-month-olds, directed to "look at the ball" in Parentese, direct their eyes to the correct picture more frequently than when the instruction is delivered in normal English.

In some ways the exaggerated, vowel-rich sounds of Parentese appear to resemble the choice morsels fed to hatchlings by adult birds. The University of Washington's Patricia Kuhl and her colleagues have conditioned dozens of newborns to turn their heads when they detect the ee sound emitted by American parents, vs. the eu favored by doting Swedes. Very young babies, says Kuhl, invariably perceive slight variations in pronunciation as totally different sounds. But by the age of six months, American babies no longer react when they hear variants of ee, and Swedish babies have become impervious to differences in eu. "It's as though their brains have formed little magnets," says Kuhl, "and all the sounds in the vicinity are swept in."

TUNED TO DANGER

Even more fundamental, says Dr. Bruce Perry of Baylor College of Medicine in Houston, is the role parents play in setting up the neural circuitry that helps children regulate their responses to stress. Children who are physically abused early in life, he observes, develop brains that are exquisitely tuned to danger. At the slightest threat, their hearts race, their stress hormones surge and their brains anxiously track the nonverbal cues that might signal the next attack. Because the brain develops in sequence, with more primitive structures stabilizing their connections first, early abuse is particularly damaging. Says Perry: "Experience is the chief architect of the brain." And because these early experiences of stress form a kind of template around which later brain development is organized, the changes they create are all the more pervasive.

Emotional deprivation early in life has a similar effect. For six years University of Washington psychologist Geraldine Dawson and her colleagues have monitored the brain-wave patterns of children born to mothers who were diagnosed as suffering from depression. As infants, these children showed markedly reduced activity in the left frontal lobe, an area of the brain that serves as a center for joy and other lighthearted emotions. Even more telling, the patterns of brain activity displayed by these children closely tracked the ups and downs of their mother's depression. At the age of three, children whose mothers were more severely depressed or whose depression lasted longer continued to show abnormally low readings.

Strikingly, not all the children born to depressed mothers develop these aberrant brain-wave patterns, Dawson has found. What accounts for the difference appears to be the emotional tone of the exchanges between mother and child. By scrutinizing hours of videotape that show depressed mothers interacting with their babies, Dawson has attempted to identify the links between maternal behavior and children's brains. She found that mothers who were disengaged, irritable or impatient had babies with sad brains. But depressed mothers who managed to rise above their melancholy, lavishing their babies with attention and indulging in playful games, had children with brain activity of a considerably more cheerful cast.

When is it too late to repair the damage wrought by physical and emotional abuse or neglect? For a time, at least, a child's brain is extremely forgiving. If a mother snaps out of her depression before her child is a year old, Dawson has found, brain activity in the left frontal lobe quickly picks up. However, the ability to rebound declines markedly as a child grows older. Many scientists believe that in the first few years of childhood there are a number of critical or sensitive periods, or "windows," when the brain demands certain types of input in order to create or stabilize certain long-lasting structures.

For example, children who are born with a cataract will become permanently blind in that eye if the clouded lens is not promptly removed. Why? The brain's visual centers require sensory stimulus--in this case the stimulus provided by light hitting the retina of the eye--to maintain their still tentative connections. More controversially, many linguists believe that language skills unfold according to a strict, biologically defined timetable. Children, in their view, resemble certain species of birds that cannot master their song unless they hear it sung at an early age. In zebra finches the window for acquiring the appropriate song opens 25 to 30 days after hatching and shuts some 50 days later.

WINDOWS OF OPPORTUNITY

With a few exceptions, the windows of opportunity in the human brain do not close quite so abruptly. There appears to be a series of windows for developing language. The window for acquiring syntax may close as early as five or six years of age, while the window for adding new words may never close. The ability to learn a second language is highest between birth and the age of six, then undergoes a steady and inexorable decline. Many adults still manage to learn new languages, but usually only after great struggle.

The brain's greatest growth spurt, neuroscientists have now confirmed, draws to a close around the age of 10, when the balance between synapse creation and atrophy abruptly shifts. Over the next several years, the brain will ruthlessly destroy its weakest synapses, preserving only those that have been magically transformed by experience. This magic, once again, seems to be encoded in the genes. The ephemeral bursts of electricity that travel through the brain, creating everything from visual images and pleasurable sensations to dark dreams and wild thoughts, ensure the survival of synapses by stimulating genes that promote the release of powerful growth factors and suppressing genes that encode for synapse-destroying enzymes.

By the end of adolescence, around the age of 18, the brain has declined in plasticity but increased in power. Talents and latent tendencies that have been nurtured are ready to blossom. The experiences that drive neural activity, says Yale's Rakic, are like a sculptor's chisel or a dressmaker's shears, conjuring up form from a lump of stone or a length of cloth. The presence of extra material expands the range of possibilities, but cutting away the extraneous is what makes art. "It is the overproduction of synaptic connections followed by their loss that leads to patterns in the brain," says neuroscientist William Greenough of the University of Illinois at Urbana-Champaign. Potential for greatness may be encoded in the genes, but whether that potential is realized as a gift for mathematics, say, or a brilliant criminal mind depends on patterns etched by experience in those critical early years.

Psychiatrists and educators have long recognized the value of early experience. But their observations have until now been largely anecdotal. What's so exciting, says Matthew Melmed, executive director of Zero to Three, a nonprofit organization devoted to highlighting the importance of the first three years of life, is that modern neuroscience is providing the hard, quantifiable evidence that was missing earlier. "Because you can see the results under a microscope or in a PET scan," he observes, "it's become that much more convincing."

What lessons can be drawn from the new findings? Among other things, it is clear that foreign languages should be taught in elementary school, if not before. That remedial education may be more effective at the age of three or four than at nine or 10. That good, affordable day care is not a luxury or a fringe benefit for welfare mothers and working parents but essential brain food for the next generation. For while new synapses continue to form throughout life, and even adults continually refurbish their minds through reading and learning, never again will the brain be able to master new skills so readily or rebound from setbacks so easily.

Rat-a-tat-tat. Rat-a-tat-tat. Rat-a-tat-tat. Just last week, in the U.S. alone, some 77,000 newborns began the miraculous process of wiring their brains for a lifetime of learning. If parents and policymakers don't pay attention to the conditions under which this delicate process takes place, we will all suffer the consequences--starting around the year 2010.