Too much, too young

EXCESSIVE STIMULATION OF YOUNG MINDS MAY NOT BE A GOOD THING, SAYS

S ANANTHANARAYAN

Current do-it-yourself child psychology has it that "catch them young" not only gives children a "competitive advantage" but also helps the brain grow at the only time in their lives that this is possible. Commercial minds have latched on and new parents wonder if they are failing the child if he/she is not in the most advertised nursery by the time he/she can walk. But parents' anxiety to give their child the best in life often starts earlier, with constant attention and aural, visual and tactile stimulation right from birth.

Christina Whiteus, Catarina Freitas and Jaime Grutzendler at the Yale School of Medicine, Connecticut, USA, report in the journal *Nature* their finding that "chronic over-stimulation early in life can permanently impair the development of tiny blood vessels in the brain". Conversely, neither reduction of sensory input nor moderately increased activity by environmental enrichment affects the same development. The context was the observation that activity-dependant development of nerve cell patterns during infancy coincides with the development of finer blood vessels in the brain. This had raised a question of whether activity of brain cells could also affect the growth of the blood vessel system.

The authors note that given the brain's high-energy consumption and susceptibility to seizure or tissue death by lack of blood supply, development of an adequate network of the narrowest blood vessels to match metabolic demands is vital. Although the major blood vessels in the brain are formed even before birth, the final development of the blood supply system continues through early infancy and is concurrent with development of the nerve cell connections of the brain. As there are common regulatory mechanisms that mediate growth of blood vessels and nerve tissue, the question of whether activity of the brain nerve cells affects the development of the blood vessel network arises and has not been investigated.

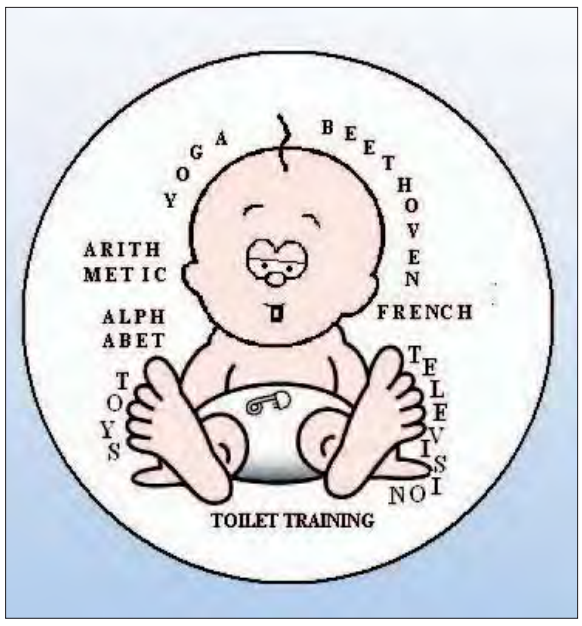
Enriched environment

To address the question, the authors investigated the effect of physical stimulation and an enriched environment, which promotes neural activity, on the development of the brain-blood vessel system in experimental mice. The first trial was of the effect of reduction of sensory inputs to the brain by trimming both the whiskers of newborn mice, on the 15th day after birth. Tests showed that this had no effect on the development of blood vessels in the part of the brain involved.

While trimming the whiskers had the effect of reducing stimulation, even moderate stimulation, by providing the young mice with an "enriched" environment, which is to provide them with tasks and puzzles or even other mice to associate with, also did not affect the rate of blood vessel growth. This trial, thus, showed that ordinary sensory and neural activity did not have an effect on brain-blood vessel development.

Further trials, however, produced unexpected results. More persistent and repeated activity as also exposure to repetitive sounds and noise over an extended period (10 hours) led to positive reduction in the development of blood vessels. This effect became greater when the stimulation by activity and sounds was extended. And what is more, the effect was specific to the part of the brain that was engaged by the enhanced activity. When the whiskers of only one side were trimmed and the remaining whiskers stimulated by an air current, for 10 hours a day for eight days, there was reduction in blood vessel development in the part of the brain associated with the stimulated whiskers. Three hours on the treadmill every day for five days resulted in reducing blood vessel growth in the area associated with motor functions.

Over the 10-day period from the 15th to the 25th day after birth, repetitive stimulation led to a reduction of 13 per cent in the branching and eight per cent in the in length of blood vessel development in the stimulated mice, as compared to the mice that were left alone.



This difference amounts to a 70 per cent reduction in the new branches and an 80 per cent reduction in the increase in length in blood vessels, as a result of the persistent stimulation. The slowdown of blood vessel development was seen to persist and did not recover even after extended over-stimulation was stopped, which shows that the effect is long lasting. In contrast, continuous stimulation of older mice did not have these effects, which seems to be natural, as branching and growth of blood vessels in the brain is not much after early infancy.

Next, the team tested the effect of epileptic seizures on the development of blood vessels. It was found that seizures induced by the drug pilocarpine, which stimulates brain cells, or by the tetanus toxin, which acts by blocking inhibiting action, led to reduction of blood vessel density in infant mice. But the injection of another drug, which blocks transmission of excitation in nerves, had no effect on blood vessels. This supports the view that it is hyperactivity that affects the development of the fine blood vessel system in the brains of newborns.

Further tests also showed that the effect on growth of blood vessels was a result of the nitric oxide that is released during neural activity. While moderate levels of nitric oxide support blood vessel formation, increased levels, due to hyperactivity, start blocking blood vessel development. In fact, it was clear that nitric oxide was the relevant factor because injecting an agent that suppressed the enzyme that helps in the production of nitric acid completely blocked the reduction in blood vessel formation that was caused by hyperactivity.

While the studies have been on newborn mice, the relevance to the development of the human brain is obvious. That very early learning, before the onset of the correct stage in development, is of little avail is well known. For instance, it is known that a child is ready to learn to read at age six. A child who is taught earlier can learn, no doubt, but may have no advantage over another child who was taught only when he/she was at the appropriate age. On the other hand, the study now reported says sensory and auditory stimulation of young children may be positively and permanently harmful, in a physiological sense, apart from psychological harm.

"These findings raise the concern that early childhood seizures or exposure to repetitive auditory and other sensory-motor stimuli, which are common in modern society, could have lifelong repercussions," the authors say in the paper.

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PLUS POINTS

Beneath the surface

Research on climate change has for a long time been focused on the temperature of ocean surfaces. But a new study has found that the intermediate waters of the Pacific Ocean have been absorbing heat 15 times faster over the past 60 years than was the case in the past 10,000 years. The study, conducted by Rutgers University, says the nature and extent of variation in subsurface ocean temperatures during climate change is unknown.

Scientists extracting shells of single-celled organisms from Indonesian waters. These were used to trace ocean temperatures of the past 10,000 years.

The researchers traced the ocean sub-surface temperature history by analysing tiny, shelled organisms called *Hyalinea balthica* belonging to the *foraminifera* group of single-celled protists. They studied the organisms present in sediment cores on the ocean floor and measured the ratio of magnesium to calcium in the shells. The warmer the water when the organism is calcified, the greater the magnesium to calcium ratio.

Using this principle, they analysed temperature variations in the Pacific Ocean from the early holocene epoch (10,000 years ago) to the present. Marine sediments were collected from the seas around Indonesia. The findings reveal that ocean temperature has changed the world over in the past 10,000 years. Yair Rosenthal, lead author of the study and professor of marine and coastal sciences at Rutgers School of Environmental and Biological Sciences, says, "We may have underestimated the efficiency of the oceans as a storehouse for heat and energy. It may buy us some time — I don't really know how much time — to come to terms with climate change. But it's not going to stop climate change."

INDU MATHI S/CSE-DOWN TO EARTH FEATURE SERVICE

Timed to perfection

Plants bear fruit just before the rainy season to ensure that produce and seed dispersal take place before the wet season. But this long-held belief was only recently put to the test. A study has utilised the difference in timings of the arrival of the southwest and northeast monsoon in India to test whether plants fruit in sync with the rains.

It is necessary that plants fruit before the rainy season. Dispersal of seeds in plants like silk cotton (left and right) would be severely impaired if the silk is wet.

Comparing a common set of plants found in regions that receive rainfall at different times of the year, the study demonstrates that peak fruiting occurs just before the rains. This ensures that germination takes place during the wet season. Thirty-three common, wind-dispersed native species were chosen for the study, including five shrubs, 11 climbers and 17 trees found in the Udupi-Mangalore region (which experiences the southwest monsoon) and in the Chennai-Pondicherry region (which experiences the northeast monsoon). The researchers examined whether the peak fruiting season of the plants were in congruence with the onset of the monsoon in their respective regions and found that plants in the southwest monsoon path bore fruit in April, ahead of the beginning of the wet season in June, while the same species, when they experience the northeast monsoon, produced fruit in August, before the wet season in October.

Millions of years of evolution have hard-wired these plants to alter their biological schedules, else the rain would wet the dispersal structures and impair dispersal. "Think of silk cotton trees and what would happen to the seeds bearing the silk when they are wet," says Uma Shaanker, co-author of the study. On the other hand, if the monsoons did not come after fruiting was complete, it could be catastrophic for the plant population. "In the common jackfruit tree, for example, seeds have a viability period of only two weeks. Thus, if the rain is late, the seeds will die," she explains.

What happens with fluctuations in the arrival of the monsoon as a consequence of climate change? "There can be a certain degree of phenotypic plasticity in plants that allows them to adjust to these fluctuations," she says.

The study — conducted by the Ashoka Trust for Research in Ecology and the Environment and the School of Ecology and Conservation, University of Agricultural Sciences, Bengaluru — was published in *Biology Letters* on 23 October.

TIASA ADHYA/CSE-DOWN TO EARTH FEATURE SERVICE

HOW CANCER DEVELOPS

IT ARISES THROUGH A MULTI-STEP PROCESS, WRITES

TAPAN KUMAR MAITRA

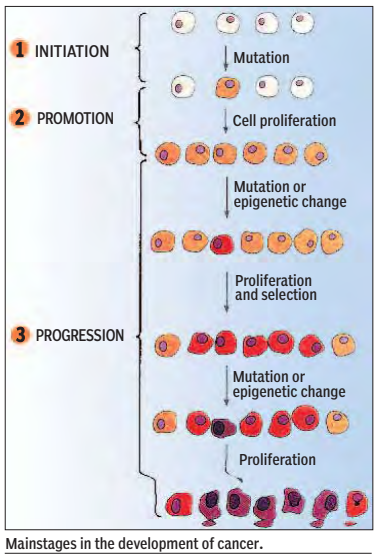
Although mutation plays a prominent role, the development of cancer requires multiple steps. Early evidence for this concept came from studies involving the behaviour of coal tar components such as dimethylbenz (a) anthracene in laboratory animals. Feeding mice a single dose of this component rarely causes tumors to develop. However, if a mouse that has been fed a single dose is later treated with a substance that causes skin irritation, cancer develops in the treated area. The irritant most commonly used for triggering tumor formation is a plant-derived substance called croton oil, which is enriched in compounds called phorbol esters. Croton oil does not cause cancer by itself, nor does cancer arise if dimethylbenz(a) anthracene is administered after the croton oil. These observations indicate that both play two different roles, which are termed initiation and promotion. During initiation, normal cells are converted to a precancerous state, and promotion then stimulates the altered cells to divide and form tumors.

In the preceding type of experiment, a year or more can transpire after feeding animals a single dose of dimethylbenz(a)anthracene and yet tumors will still develop if an animal's skin is then irritated with croton oil. This means that the former created a permanently altered, initiated state in cells located throughout the body and that the subsequent administration of croton oil acted on these altered cells to promote tumor development. The ability of chemicals to act as initiators correlates with their ability to cause DNA damage, suggesting that the permanently altered, initiated state is based on DNA mutation.

In contrast, promotion is a gradual process that requires prolonged or repeated exposure to a promoting agent. Investigation of a wide variety of promoting agents, such as the phorbol esters in croton oil, has revealed that their main shared property is the ability to stimulate cell proliferation. When a cell that has sustained an initiating mutation is exposed to a promoting agent, it is therefore stimulated to divide and the number of mutant cells increases. As proliferation continues, natural selection tends to favour cells exhibiting enhanced growth rate and invasive properties, eventually leading to the formation of a malignant tumor. The time required for promotion contributes to the lengthy delay that often transpires between exposure to an initiating carcinogen and the development of cancer.

Initiation and promotion are followed by a third stage, known as tumor progression. During this stage, tumor cell properties gradually change over time as they acquire more aberrant traits and become increasingly aggressive. The driving force for tumor progression is that cells exhibiting traits that confer a selective advantage — for example, increased growth rate, increased invasiveness, ability to survive in the blood- stream, resistance to immune attack, ability to grow in other organs, resistance to drugs, evasion of apoptosis, and so forth — will be more successful than cells lacking these traits, and so will gradually tend to predominate.

While it is easy to see why cells exhibiting such traits tend to prevail through natural selection, this does not explain how the aberrant traits originate in the first place.



Mainstages in the development of cancer.

One source of new aberrant traits is further DNA mutations that occur after the original, initiating mutation. New traits can also arise from changes in the expression of normal genes. The term epigenetic change is used when referring to such alterations in the expression of a gene rather than a change in the structure of the gene itself — in other words, activating or inhibiting the activity of a normal gene without mutating it. Tumor progression is made possible by a combination of DNA mutations and epigenetic changes, accompanied by natural selection of those cells that acquire advantageous properties through these mechanisms.

Does the body have any defence mechanisms for protection against the development of metastases? One possibility is the immune system, which has the ability to attack and destroy foreign cells. When cancer cells circulate in the bloodstream, where the cells of the immune system travel in large numbers, they are especially vulnerable to attack. Of course, cancer cells are not literally of "foreign" origin, but they often exhibit molecular changes that might allow the immune system to recognise the cells as being abnormal.

Animal experiments suggest that in some cases, attack by the immune system does limit the process of metastasis. One such study by Michael Feldman and Lea Eisenbach involved two strains of mouse lung cancer cells: D122 cells that metastasise with high frequency and A9 cells that rarely metastasise. In general, the immune system's ability to recognise cells as foreign or abnormal depends on the presence of cell surface proteins called major histocompatibility complex (MHC) molecules.

When Feldman and Eisenbach examined these molecules carried by the two lines of tumor cells, they discovered a striking difference: A9 cells carried two types of MHC (called H-2K and H-2D), whereas the D122 cells expressed only one form (H-2D).The discovery that D122 and A9 cells carried different cell-surface MHC molecules raised an important question: was the differing metastatic behaviour of the two cells related to the immune system's ability to recognise and attack the two cell types? This issue was investigated by injecting A9 and D122 cells into separate groups of animals and monitoring the production of cytotoxic T lymphocytes (CTLs), a class of immune cells specialised for attacking foreign and abnormal cells. The animals were found to produce numerous CTLs targeted against A9 cancer cells, but few CTLs targeted against D122 cells.

Why do CTLs attack A9 cells more readily than D122 cells? The most obvious possibility is that the immune system recognises the H-2K MHC molecules, which are carried by A9 cells but not by D122 cells. This hypothesis was tested by introducing purified DNA containing the H-2K gene into D122 cells, thereby causing the D122 cells to produce the H-2K form of MHC. As predicted, the altered D122 cells expressing H-2K exhibited a reduced capacity to metastasise when injected into mice, suggesting that the presence of H-2K made the cells more susceptible to immune attack.

However, the primary tumor at the injection site grew normally, implying that tumor cells attempting to metastasise through the circulatory system are more susceptible to immune attack than are tumor masses lying outside the bloodstream.

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How life may have developed

STEVE CONNOR REPORTS ON NEW RESEARCH INTO THE 'DEEP BIOSPHERE' THAT INDICATES THE FIRST REPLICATING LIFE FORMS ON EARTH MAY HAVE ORIGINATED DEEP UNDERGROUND

How life on Earth came into existence is still one of the greatest mysteries in science but new research into the "deep biosphere" indicates that the first replicating life forms on the planet may have originated deep underground rather than, as is commonly believed, on the surface. Scientists have now discovered microbes living and reproducing as deep as five kilometres below ground and studies have shown that they are likely to have survived in complete isolation from the surface biosphere for millions and perhaps even billions of years.

One of the latest studies into the deep biosphere has found that these microbes form a distinct subsurface community of genetically similar individuals despite living on opposite sides of the world. This global similarity of such an isolated life form suggests that they may have evolved directly from a common ancestor that lived at the period when life on earth originated — some 3.5 billion years ago.

An increasing number of researchers believe that life could have first got going in the tiny cracks of underground rocks, fuelled not by the energy of sunlight but by chemical fuel in the form of hydrogen and methane that can be produced in certain types of rock under high temperatures and pressures.

The latest discovery of a closely-related, global community of microbes in the deep biosphere lends further support to the idea that life originated not in the "primordial soup" of surface lakes and seas, but in the tiny water-filled fissures found in underground rock, said Matt Schrenk of Michigan State University.

"Two years ago we had scant idea about what microbes are present in subsurface rocks or what they eat. Since then, a number of studies have vastly expanded that database," he said. "We're getting this emerging picture not only of what sort of organisms are found in these systems but some consistency between sites globally — we're seeing the same types of organisms everywhere we look."

The study, presented recently to the American Geophysical Union in San Francisco, compared DNA sequences of hydrogen-eating microbes extracted from rock fractures deep below North America, Europe, South Africa and Japan. To their surprise, the scientists found that they were closer than 97 per cent similar — making them virtually the same species, Schrenk said.

Hydrogen microbes have been found between four-five kilometres in a Johannesburg mineshaft, and are believed to live in even deeper locations below the seabed.

However, other researchers have since pointed to problems with this scenario, such as the fact that the surface of the planet 3.5 billion years ago was subjected to intense ultraviolet radiation, which would have quickly destroyed complex biological molecules exposed to the light, and to asteroid bombardment, which could have easily eliminated life at the surface before it had chance to evolve.

"It is conceivable that life arose not in a warm, little pond, but sheltered in a warm, little fracture below the surface of the crust, or in the deep oceans, protected from the tumultuous events on the surface," said Barbara Sherwood Lollar of the University of Toronto, and a colleague of Schrenk's on a 10-year research project called the Deep Carbon Observatory.

New research into the "deep biosphere" indicates that the first replicating life-forms on the planet may have originated deep underground.

Scientists have found that underground microbes can survive temperatures as high as 120 Celsius and pressures 50 times greater than at the surface, which could have industrial and medical applications. "There's a lot of potential to utilise their genes and the enzymes they code for," Shrenk said.

Knowledge of the earth's deep biosphere and how it survives such environmental extremes could also help astrobiologists searching for life on Mars, where the planetary surface is known to be hostile for living organisms.

THE INDEPENDENT