Recent Developments in Science and Medicine

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Fat rat fathers have daughters with diabetes

Male rats fed on a high fat diet develop problems metabolising glucose and intolerance to insulin compared to male rats fed on their normal diet. Alarmingly, researchers in Australia have now shown that the daughters of the fat father rats also become glucose-intolerant by six weeks of age (rat puberty) and show impaired insulin secretion by 12 weeks. These are symptoms of type II diabetes. The offspring of the non-obese rats did not develop these symptoms.

The father rats must be transmitting the symptoms of type II diabetes to their daughters through alteration of genes in their sperm, viz., epigenetic modifications superimposed on the sperm DNA affecting the activity of certain genes. Indeed, the authors detected changes in the activity of over 600 pancreatic islet genes in the affected daughters. It is curious that there is no report on what happens to the sons of the fat fathers and why more work is required to know this. Perhaps heritable diabetes is due to epigenetic changes in the sperm carrying the X chromosome rather than that carrying the Y chromosome,

A lot of research has been done to show the damaging effect of the mother's poor diet and obesity on her offspring's metabolism and obesity but there has been less research on the paternal influence. We do not know whether these observations in the rat also extend to the human. We do know that the increasing global prevalence of human obesity is correlated with the early emergence of type II diabetes and that, if either parent is obese, this increases the risk of obesity in their offspring.

The transmission of epigenetically altered genes through the germ line (sperm or egg) is a relatively newly discovered phenomemon which opens the way to inheritance of acquired characteristics – or so-called Lamarkian inheritance. My own work showed that, following fertilization, the genomes from the egg and sperm undergo a global DNA demethylation (erasure of epigenetic programming) such that the cells of the early embryo are returned to the tabula rasa default stem cell state ready to differentiate into all the different types of cells in the fetus and new individual. This global DNA demethylation, which we called 'deprogramming', removes most of the epigenetic changes that might have accumulated on the parental genomes due to the way the parents lived their lives and interacted with their environment. However, we now know that some epigenetic modification of genes survives the deprogramming (erasure) event in early development of offspring embryos and this can alter their phenotype irrespective of further direct environmental exposure. The interesting question is whether this epigenetic change causing heritable diabetes can survive to be transmitted to subsequent generations.

References

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Climate change by space tourism

Commercial space flights are likely to discharge just as much soot, or black carbon, into the environment as current global aviation. Ross and colleagues (Aerospace Corporation. LA, California) estimate that emissions from private rocket launches would persist high in the stratosphere, potentially altering global atmospheric circulation and distributions of ozone. The simulations show that the changes to Earth's climate could increase polar surface temperatures by 1°C, and reduce polar sea ice by 5 to 15 per cent.

Nevertheless, space travel is on the way. Virgin Galactic expect to make up to two launches a day in the next three years from the launch site at Spaceport America in New Mexico and NASA is financing private companies to take astronauts and cargo into orbit. The problem is that there is no rain in the stratosphere to wash away the black soot particles. The black carbon layer will cause temperature and ozone levels to decrease in the tropics and increase at the poles. Stratospheric pollution will add to the already existing problem of the debris in space endangering our astronauts. Clearly more discussion is necessary between scientists, engineers and members of the private space-flight industry.

Reference

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Gene therapy helps depressed mice

It is generally accepted that defects in the serotonin signalling pathway in the brain are associated with depression and that antidepressants act by causing an increase in serotonin. Researchers, at the Department of Neurological Surgery, Weill Cornell Medical College, New York, have now injected into mouse brains a gene called p11, which causes an increase in serotonin receptors on the cell surface. Mutant mice lacking this p11 gene exhibit depressive behaviour - they are less active when picked up and swim slowly when placed in water. The researchers injected a virus vector containing the p11 gene into a part of the brain known to require this gene - the nucleus accumbens - and this reversed the depressive behaviour of the mutant mice

Turning to humans, they showed that the nucleus accumbens of postmortem brains of depressed individuals had much lower levels of p11 than that of their non-depressed counterparts. This suggests that reversal of the low level of p11 in this area of the human brain could reduce depressive symptoms.

However, it is known that animal models of depression are not readily translated to the human. In addition, the experiments with the mice were more about pleasure in activity and not the anxiety and stress often associated with human depression. The approach is very invasive and long-term effects are unknown and irreversible. Nevertheless, in the future, the treatment may work for severely affected people who are not helped by drugs. The scientists are also investigating a gene therapy approach into the brain for Parkinson's disease.

Reference

Alexander B, Warner-Schmidt J, Eriksson T, Tamminga C, Arango-Lievano M, Ghose S, Vernov M, Stavarache M, Musatov S, Flajolet M, Svenningsson P, Greengard P, Kaplitt MG. (2010). Reversal of depressed behaviours in mice by p11 gene therapy in the nucleus accumbens. Sci Transl Med. 2::54ra76.

Tracking marine life with Tethys, the underwater robot

Monitoring underwater life in the oceans is difficult from the surface as the ocean currents keep moving things about and changing local environments. Sandeep Ravindran reports on the robot, Tethys, in the journal, Nature, in November 2010. Tethys is an underwater robot which can travel with speed over large distances and for a long time. The robot is designed specifically to follow marine life for many months to record its movement and behaviour and also the properties of the water around it. It can travel hundreds of miles from shore and send information back to the scientist by satellite so that oceanographers can carry out their experiments on land. Tethys has currently integrated itself in an algal patch in Monterey Bay in California and is tracking the migration of the algal blooms. The robot will be involved in other projects in the future such as monitoring the effects of whirlpool eddies on the ocean environment and sampling the complexity and diversity of life in the ocean over long distances and time scales. In future, Tethys will be further modified to bring back water samples from different locations, analyse DNA to identify microorganisms in the water, and incorporate sensors to measure ocean carbon and acidification to monitor climate change. Tethys offers a means to study wildlife in a more continuous and less invasive way than the stressful tagging of animals.

Reference

Sandeep Ravindran (2010) Underwater robot can follow marine organisms over record distances. Versatile vehicle can spend months studying ocean ecology. Nature. 1st November 2010

The brain-machine interface

Our brains are constantly bombarded with thoughts, images, smells and other sensations. It is all too much. But recent research by Moran Cerf (California Institute of Technology, Pasadena) has shown that we can, and do, apply conscious thought to focus on particular stimuli and fade out what we want to ignore. The study was on 12 volunteer patients awaiting brain surgery for epilepsy (neurosurgeon, Itzhak Fried). To identify the region responsible for their epilepsy, their brains were wired up to a computer by implanting an array of 64 tiny electrodes in the medial temporal lobe (which includes the hippocampus associated with memory) and then waiting for epileptic symptoms to oocur.

Neuroscientists, collaborating with Fried, used the waiting time of these patients in the study on mind control. The volunteer patients were asked to select one of two images of various celebrities on a screen. The subjects were able to enhance the image they selected successfully by controlling the firing rates of individual neurons with the recognition, or even their imagination, of that one particular person. In other words, individual neurons uniquely and reliably responded to one of the images and this information was transmitted to the computer. Even when two images were 50 per cent faded out and superimposed, the subjects could enhance their preferred image within ten seconds just by thinking about it. A decoder in the computer enhanced the image whose neuron was firing more quickly and faded the image whose neuron was firing more slowly. Removal of the 'brain-machine interface' feedback greatly diminished their success. The experiments show how the brain shapes our perception of reality.

In the future, such machines wired into the brain may allow 'locked in' and paralysed patients to communicate and move robotic limbs via a computer reading the activity of neurons in their brains.

Reference

Cerf M, Thiruvengadam N, Mormann F, Kraskov A, Quiroga RQ, Koch C, Fried I. (2010) On-line, voluntary control of human temporal lobe neurons. Nature 467:1104-1108.

Coral bleaching

Corals are an important part of the marine ecosystem. Coral bleaching occurs when corals expel small symbiotic algae when they experience stress due to prolonged increased temperature, ocean acidification, and/or local factors such as surface run-off and storm intensity.

Massive coral bleaching (over 80 per cent of corals affected) occurred in the Caribbean in the year 2005 due to the increased temperatures in the Atlantic Ocean and Caribbean Sea - the highest thermal stress in 20 years. Mark Eakin (US National Oceanic and Atmospheric Administration's Coral Reef Watch, Maryland), together with several hundred collaborators, have carried out an extensive coral survey in many different areas using satellite data and field surveys. They observed that, as well as the Caribbean, bleaching occurred in many other areas

for the first time, e.g., Gulf of Mexico and Virgin Islands. Corals can recover from bleaching, but in many places it is likely that bleaching is happening faster than the reefs can recover. There is concern that widespread coral bleaching in the year 2010 will be even worse due to weather patterns, and effects of recent El Niño and La Niña events, combined with overall warming due to climate change. The researchers predict even more drastic coral bleaching in the future unless atmospheric and ocean CO2 levels are brought under control. If sea temperatures cannot be stabilised, researchers may have to save small plots of important coral by shading with cloth or pumping cool water from the depths over the shallow reefs.

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Telomerase - the fountain of youth?

The ends of each of our 46 chromosomes in the nucleus of our cells have a specific sequence called the telomere that contains repeated units and is variable in length. Young cells have long telomeres on the end of chromosomes but every time cells divide their telomeres shorten and, eventually, the cells stop dividing and die. The enzyme that maintains the telomeric sequence is called telomerase. Aging is associated with less and less of this enzyme. Telomerase also prevents decline in certain cells, such as stem cells, by lengthening telomeres. Could activation of the telomerase enzyme slow cell ageing?

Mice were genetically engineered by Ronald DePinho (Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts) to lack the enzyme telomerase. These mice age prematurely. As their telomeres progressively shorten, their fertility declines, age-related conditions set in (such as osteoporosis, diabetes and neurodegeneration) and they die young. However, these dramatic effects are reversible. The inactivated telomerase was engineered in such as way that it could be switched back on again by feeding the mice a chemical called 4-OHT. After switching the enzyme back on for a month in the adult prematurely aging mice, they were rejuvenated.

The findings suggest possible intervention to increase telomerase activity for some disorders in the human characterized by premature ageing and also for age related disease. Could normal human aging be reversed by reactivation of this enzyme where it has stopped working? It is always difficult and dangerous to extrapolate experiments from mice to human. Also, importantly, it is known that cancer cells have increased telomerase activity. So increasing telomerase may speed the growth of cancers. The experiment really needs to be done to increase telomerase activity in normal mice to see whether it prolongs their life and whether there is an increase in cancer incidence in these mice.

Reference

Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, Sahin E, Kost-Alimova M, Protopopov A, Cadiñanos J, Horner JW, Maratos-Flier E, Depinho RA. (2011). Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature 469:102-106.

Chemistry, archaeology and biblical history

Chemists and archeologists are working side by side in digs of an important site - Tel Megiddo. This work may test the historical truth of the Bible's account of the first united Kingdom of Israel. Was Tel Megiddo, now a dusty mound overlooking Israel's Jezreel valley, a regional centre of power in the kingdom of David and Solomon during the 11th and 12th Centuries BC?

Archaeologists identify strata — buried layers representing particular periods of habitation. A black stripe, for example, might be a burn layer — evidence of a hearth, or of the ransacking of a city, depending on its size. Artefacts and pottery embedded in strata can also serve as markers for defining and dating them. Chemical analysis, alongside the archaeology, can add many more details to the picture and distinguish strata that may look the same and also give more refined evidence of age. Small samples are analysed in an infrared spectrometer on site to provide the diggers with immediate clues as to the nature of the stratum. Chemical analysis can distinguish between soil layers, e.g., the distinctive origins of seemingly identical layers of calcite, whether from burnt wood, or from limestone slaked to make lime for construction. This helps archaeologists to distinguish between a floor, a wall or a kiln. Similarly, phytolith layers rich in a form of silica from plant cells distinguish where vegetation grew, or was stored, or in an area used as an animal enclosure. Other analyses may involve a pottery storage jar full of grains of wheat - the kernels can be sent abroad to a particle-accelerator facility for radiocarbon dating. Having the chemists on site can help archaeologists to make faster decisions about where to excavate and what samples to collect, and, ultimately, to yield more useful analyses.

However, whether biblical narratives can be challenged by science is a difficult area. One would hope that the spurious ‘science vs. religion’ controversy is not driving the research.

Reference

Haim Watzman (2010) Chemists help archaeologists to probe biblical history. Collaboration establishes a new approach for teasing out clues hidden in the soil. Nature 468:614-615.

The placebo effect: the role of patient belief

The placebo effect describes the improvements seen when patients – unknowingly – are given dummy pills or sham treatments but believe it will do them good. This is a very real physiological effect; it is not just about patients ‘feeling’ better. The nocebo effect is the opposite; patients see poorer outcomes as the result of doubts about a medical treatment.

A new brain imaging study led by Irene Tracey (Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University) and colleagues (University Medical Center Hamburg-Eppendorf, Cambridge University, Technische Universität München) has shown how manipulating expectations can influence response to an active drug.

In the study, 22 healthy adult volunteers were placed in an MRI scanner and heat applied to the leg at a level where it begins to hurt. An intravenous line for administration of a potent opioid drug for pain relief was also introduced. When the drug was given without the participant’s knowledge the pain was rated to decrease from a level of 66 to 55. Then the patients were told the drug was being administered (although no change was made) and their experience of pain

decreased further to 39. Then the participant was told the drug was being stopped (though again no change was made) and their pain intensity increased to 64, i.e., equivalent to the experience of pain at the beginning without any opioid drug at all. The MRI imaging confirmed that the brain's pain networks correlated with the participant's experience as reported by them. This showed that the volunteers really did experience different levels of pain when their expectations were changed, although the administration of pain relief remained constant throughout.

The research suggests that doctors need to consider addressing patients' beliefs about the effectiveness of any treatment they administer.

Reference

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And see also -

Benedetti F, Carlino E, Pollo, A. (2011). How Placebos Change the Patient's Brain. Neuropsychopharmacology 36:339–354

Mice bred with two dads

This was likely to happen eventually. Scientists can now reliably derive and culture embryonic stem cells outside the body – either from pluripotent cells of the embryo itself, or cells derived from eggs injected with a nucleus from any cell of the body, or by creating induced pluripotent cells by injection of pluripotent genes into a somatic cell. The scientists used the latter method to create induced pluripotent stem cells (iPS cells) from a male (XY) mouse (Father 1). These cells were used to isolate subclones that had spontaneously lost the Y chromosome to become genetically female (XO) cells in culture. These male-derived XO stem cells were then combined with a female embryo and the chimaeric embryo replaced in the mother mouse to produce live chimaeric female mice offspring with some of the XO cells from the original cultured male cells in the germ line, i.e., the female mouse has male-derived XO eggs in her ovary. When this chimaeric female is bred with a genetically distinct male (Father 2), and her XO eggs are fertilised, the resulting progeny possess genetic information that was equally derived from both fathers. In other words, these progeny have two male parents. The application of this technology to allow two human males to produce a child is currently very unlikely due to the instability and variability of human iPS cells in culture and ethical implications of creating human chimeras which, in any case, would definitely be illegal.

Reference

Deng JM, Satoh K, Wang H, Chang H, Zhang Z, Stewart MD, Cooney AJ, Behringer RR.(2011). Generation of viable male and female mice from two fathers. Biol Reprod. 84:613-618.

Is sex selection illegal and immoral?

PGD, or preimplantation genetic diagnosis, is the diagnosis of a genetic disease in a cell or a few cells, biopsied from an early embryo produced by IVF, and replacing only those embryos free from disease back in the mother to initiate a pregnancy. PGD avoids the need for therapeutic abortion of a much wanted baby if a later test during pregnancy (e.g., amniocentesis) shows that the fetus is affected and, if born into the world, the baby will suffer and die. PGD may be offered to families who already know they are at risk of having a baby with a serious genetic disease. Our own work developing highly sensitive single cell molecular assays pioneered this technique in the 1980's and the first PGD baby diagnosed for a single gene defect was born in 1992. With the spread of application of this procedure worldwide, new developments arise with significant ethical implications, such as saviour siblings or sex selection. In the first case - saviour sibling - the parents wish to choose an embryo matched immunologically to an existing child with a life threatening disease so that the umbilical cord blood of the new pregnancy can be used to save the older child. With sex selection, PGD is used medically to make sure that a boy baby is avoided if the disease gene is on the X chromosome, such as Duchenne Muscular Dystrophy or Lesch Nyhan disease.

However, the other reason for sex selection is because the family already has a number of children of one sex and want the new baby to be of the other sex. Stevienna de Saillec considers the ethics of this latter reason for sex selection ('family balancing') in a recent edition of BioNews. This is an extremely controversial issue in the UK where the procedure is currently illegal. Public consultation in 2003 revealed that 80 per cent were against sex selection for non-medical reasons. The procedure is allowed in the USA but legal in only one country in Europe - Northern Cyprus. Although social sex selection is illegal in the UK, the Human Embryology and Fertilisation Authority (HFEA) does not have the power to penalise UK clinics for recommending overseas services which are not legal here. UK clinics may also be involved in preparing patients for transfer to services in other countries (known as 'Transport IVF') possibly funded by the NHS. Should services in this country support a healthy woman to undergo painful, risky and expensive procedures in order to have a baby of a chosen sex elsewhere? Whatever the legal situation, couples determined to use services banned in this country will travel to a place where they are permitted. But is it lawful for British clinics to profit from partial involvement in procedures which would be illegal if wholly carried out at home? In considering these questions we should note our ethical position with respect to 'other people' and what we would want for ourselves in their shoes.

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