Recent Developments in Science and Medicine

Marilyn Monk

Some worms are good for you

Humans have co-evolved with their intestinal worms. Like bacteria, some worms reside harmlessly in the gut whereas others can cause disease. It is reasonable to assume that some worms, like helminths, may have evolved to provide important protective functions for themselves and for their host. However, with the development of improved hygiene, clean food and water, and the use of drugs to treat diseases - mostly due to harmful pathogenic bacteria – intestinal worms have, to a large extent, been eliminated in developed countries. At the same time, new autoimmune diseases have emerged – for example, inflammatory bowel disease.

In less developed countries, inflammatory bowel disease is much less frequent and one hypothesis is that helminth worms provide protection by modulating the host immune system. Blum, Weinstock and co-workers (Department of Internal Medicine, Tufts Medical Center, Boston, USA) have shown, in a mouse model of inflammatory bowel disease, that injection of several thousand helminth eggs prevents colitis by altering immune cell function (regulatory T cells and dendritic cells) in the intestine. The worms also seem to promote the growth of gut probiotic microorganisms beneficial for intestinal health.

Currently, several clinical trials are in progress in which patients are colonized with intestinal worms to treat autoimmune diseases such as ulcerative colitis and Crohn's disease. Early evidence indicates that the treatment may be safe and effective.

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Light-dark cycle regulates mood

Living organisms adjust their circadian rhythms (biological clocks) and their sleeping/waking cycles to the daily solar cycle. It is known that changes that introduce irregular light and dark periods affect mood and cognitive function. Shift work, travel across time zones (jet lag), changes in day length with country of residence and season (lengthening dark or light periods in the day) are all associated with depression and cognitive deficits. Often the changes that introduce the aberrant light-dark periods are associated with sleep deprivation and sleep disturbance and it has not been known whether an aberrant light-dark cycle alone can directly affect mood and cognition. LeGates and co-workers (Department of Biology, Johns Hopkins University, Maryland, USA) have used a mouse model to test this by changing the light-dark periods and monitoring mood and cognitive functions, sleep, and circadian rhythms.

Normally, the mice are housed with 12 hours light and 12 hours dark. This was changed to a 3.5 hour light and 3.5 hours dark cycle. The mice showed depressed behaviour and compromised cognitive function (learning deficits) with these irregular light schedules. They performed better when given antidepressants indicating that the cognitive deficits were likely to have arisen from their depressed mood. Mice exposed to the aberrant light cycle maintained daily corticosterone rhythms which showed that their circadian rhythms were not disturbed. Their sleep pattern was also normal. The mechanism regulating the alteration of mood and cognitive function required intrinsically photosensitive retinal ganglion cells in the eye. Mice deficient in these cells showed no ill effects of aberrant light-dark cycles. The work provides convincing evidence that abnormal light-dark exposure can directly affect mood and cognitive function through intrinsically photosensitive retinal ganglion cells without changing the underlying circadian timing system and normal sleep pattern.

Reference

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Aberrant light directly impairs mood and learning through melanopsin-expressing neurons.
Nature 491: 594–598 (2012)

Simplifying complexity

When analysing a complex system - for example, a living organism or a social network - we know that only a few parameters and characteristics (outputs) are accessible for us to observe and much is hidden from view. In order to work out the whole it would seem that we would have to completely take it apart. However, this may not be necessary, nor useful, and instead we deduce a picture of the whole from the observable outputs. Some of the accessible outputs are more important than others in this endeavour. Network-theory researchers, Liu, Slotine and Barabaasi (Center for Complex Network Research and Department of Physics, Northeastern University, Boston, USA), present a graphical approach, derived from the dynamical laws that govern a system, to reveal the components (sensors) that are necessary and sufficient to reconstruct the full internal state of a complex system. Within the system, there are clusters of strongly connected components and instances where one particular component determines the activity of the others. They applied their mathematics to all the biochemical reactions governing the metabolism of a human cell and showed that variation in only 10 per cent of the 2,763 metabolites involved determines the levels of all the other metabolites. Thus a network is reduced to the really important component parts that drive the system's behavior. The approach offers inroads to explore a wide range of natural, technological and socioeconomic systems - for example, to determine the people with major influence in social networks, or predict the outcome of an election, determine a particular species to follow in order to predict and track changes in an ecosystem, or which of many associated gene changes to follow to predict outcome in a particular cancer.

Reference

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Proc Natl Acad Sci U S A. 10:2460-2465 (2013)

Climate change and the expansion and collapse of the Mayan empire

The Mayan civilisation (300 AD to 1000 AD), which occupied much of present day Mexico and Central America, left a plethora of historical records carved into dated stone monuments. The civilisation flourished and expanded into many kingdoms from 300 to 600 AD during a period of bountiful rainfall and then collapsed during the period 600 AD to 1000 AD, a time of drought. The association between the historical records charting the rise and fall of the Mayan empire with changes in the climate has been controversial. Now, Douglas Kennett and colleagues (Pennsylvania State University, USA) have used the changing composition of rapidly growing stalagmites from Yok Balum Cave, Belize, to provide accurate long, continuous records to precisely date the climate record for the past 2000 years. Historical rainfall in the Mayan lowlands is calculated by measuring the incorporation of oxygen isotopes into the stalagmite from rainwater that seeped into the cave from the ground above. The method has much greater precision and accuracy than carbon dating. From a comparison of this climate record with historical events, they propose that high levels of rainfall favoured population expansion and the proliferation of political centres between 440 and 660 AD. This was followed by arid conditions between 660 and 1000 AD and extended drought between 1020 and 1100 AD. The authors conclude that climate change led to decline in population and collapse of the Mayan empire. The study could have important implications for climate modelling.

Reference

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Adaptation to climate change rather than prevention?

Ten years on from the Kyoto conference it is clear that nations have done little to prevent the advance of climate change. Unacceptable carbon emissions continue and, according to the experts, storms and floods, heatwaves and droughts, will increase, and with greater severity, as the climate warms. At the time of the Kyoto conference, it was agreed that the causes of climate change must be held in check and the idea of adaptation was dismissed. However the prevention measures agreed at Kyoto do not seem to be making a difference and greenhouse-gas emissions are increasing at an unprecedented rate. Locally, where disasters have struck already, there is more urgency to adapt to climate change and climate researchers and policy-makers are being forced to explore ways to defend their environment against the inevitable changes. It seems to take a disaster to happen to stir people into action.

Adaptation encompasses many different approaches and is location specific – building sea walls, dams, raising houses, or moving whole towns and villages elsewhere away from rising sea levels. An excellent review by Olive Hefferman in Nature November 2012 addresses these issues. Certain regions are already marked as particularly vulnerable. Bangladesh is extremely vulnerable to storms and flooding; hundreds of thousands of people have died. The country is building sea walls, growing salt resistant crops, planting mangroves to protect against erosion and storing fresh water. Like Bangladesh, the nations of sub-Saharan Africa are also particularly vulnerable to climate change. Between 1965 and 1998, Mozambique experienced 12 major floods, 9 major droughts, and 4 major cyclone events and the Mozambique government is working on a long-term strategic adaptation plan. The problem in many vulnerable countries is poverty and lack of funding.

But climate change disasters are not limited to poorer countries. In Australia, severe droughts over the last decade have stirred action with the construction of a desalination plant

in Victoria and a pipeline to bring river water to arid areas. However, there are those who criticise the efficacy of these projects arguing that the billions of dollars might be better spent harvesting rainfall and recycling domestic water waste. Superstorm Sandy brought floods, black outs, flooding of subways and pollution of water supplies to New York and 50 billion dollar economic losses. In the United Kingdom, droughts leading to water restrictions alternate with record rain fall and flooding. Heatwaves - likely to increase in frequency and duration - can also cause many deaths. France is in the process of developing a heart wave warning system (15,000 people died from heat in France in 2003) and mobilization of personnel to care for the vulnerable.

One of the major problems of the adaptation approach is uncertainty as to when and where and what disaster will strike next. Uncertainty makes it difficult to decide on the best adaptation strategy to take. Also, climate change is a global issue but richer countries have more resources to adapt to the consequences increasing the rich-poor divide. It would be clearly better, and economically more sound, if we could find a strategy to deal with the causes of climate change now rather than the effects later. Measures must be taken to enforce compliance with agreements established between nations.

Reference

Olive Heffernan.
Adapting to a warmer world: No going back.
Nature, 28 November (2012)

Early life stress and raised cortisol in young girls correlated with altered neural connections and anxiety and depression in their teenage years

It has been known for some time that early life stress is associated with later psychological, emotional and physical problems. Now Burghy and co-workers (Waisman Laboratory for Brain Imaging and Behaviour, University of Wisconsin-Madison, USA) have followed girls from early life into teenage years. Girls suffering early life stress, and showing an associated increase in salivary cortisol levels at age 4, were examined 14 years later for levels of anxiety and, by functional magnetic resonance imaging, for brain function.

The teenage girls (57 eighteen year olds) who had raised cortisol levels at age 4 showed altered connections in the brain, viz., decreased connectivity between the amygdala (a region of the brain processing fear and emotions) and the ventromedial prefrontal cortex (an outer region regulating the amygdala's stress response). The decreased connectivity is correlated with increased anxiety. The study shows that increased cortisol when young affects brain function 14 years later. Early life stress not associated with increased cortisol did not have this effect - some children are resilient. It is not known why anxiety and mood disorders are more common in women. Both boys and girls may suffer stress in childhood but the early stress leads to different consequences in later life. Males are more likely to suffer later from antisocial behavior and substance abuse.

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Global catastrophes

Is the end nigh? It is reasonable to predict that there will be an end but it is impossible to say when. In a report in the journal *Nature*, Nicola Jones examines the unpredictable natural catastrophes that could bring disaster to life on our planet – asteroid impacts, super-volcanoes, solar flares, γ-ray bursts and tsunamis. Impact with an asteroid 10 kilometres wide wiped out the dinosaurs 66 million years ago - the Cretaceous–Paleogene extinction. We have been recently reminded of the danger from the skies by the small meteor exploding in an air burst over Russia recently, and another one passing earth at a distance of the moon's orbit last month. Other natural threats from above are occasional huge solar flares which have happened in the past; this may not be an extinction event but today would have dire consequences due to wipe out of satellites and power stations. Similarly, a blast from a nearby (within our Milky Way) γ-ray burst caused by collision of two black holes, or neutron stars, could wipe out Earth's protective ozone layer.

Tsunamis are a natural threat on our planet and the recent devastation in Japan is a reminder. They may be caused by earthquakes or huge chunks of land slipping into the sea. Giant submarine landslides, for example the Mauna Loa volcano of Hawaii 100,000 years ago, can launch a wave hundreds of metres high. There are other examples, but when the next one will occur nobody knows. Then there are giant eruptions from volcanoes. One of the most recent giant eruptions of a super-volcano - Toba in Indonesia 74,000 years ago - may have started the last ice age. Other super-volcanic systems are being monitored in Italy, Yellowstone USA, and New Zealand. The threat of another super-eruption is real and there may be little warning. Another global threat recently highlighted by Fisher and colleagues (Department of Infectious Disease Epidemiology, Imperial College, London) is pathogenic fungi which decimate crops, kill insects and animals, and cause an estimated 70 per cent of regional extinctions. The Irish potato famine in the 1840's was caused by *Phytophthora infestans* – an organism grouped with fungi - and there are many other examples of increasing number of virulent infectious diseases in natural populations in both animal and plants.

However, perhaps the greatest threat to our survival today is CO2 concentration in our atmosphere warming and acidifying our oceans and melting ice caps. The greatest threat to our survival is *us* and our inability to use more eco friendly energy sources.

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Emerging fungal threats to animal, plant and ecosystem health.
Nature, 484:186-194 (2012)

Nicola Jones.
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Nature 493:154-156 (2013)

Is scientific genius extinct?

In Nature in January this year, Dean Keith Simonton asks whether scientific genius is extinct. One factor that immediately occurs to me is that genius might have become less noticeable now that scientific research involves huge advances in technology and large teams of scientists across the world collaborating to broaden and deepen knowledge in specific specialist fields. Published papers have many authors - it is rare now to see publications of new findings with only one or two authors. Also, the current scientific climate is not encouraging to the adventurous and imaginative scientist. As I see it, most scientific endeavour is piling more facts upon an existing pile of facts initiated on some arbitrary basis that could be leading in the wrong direction. Few scientists work on the edge of the known and unknown and very few are seen to be asking questions in the unknown. Such speculation is not encouraged in the lab

where only hard verifiable discoveries ('reproducible by anyone anywhere') are acceptable and PhD students must be given a 'safe' project sure to produce some results for their theses from the outset.

Dean Simonton defines the creative scientist as one who 'contributes ideas that are original and useful'. He defines a scientific genius as one who contributes ideas that are 'original, useful and surprising'. Most scientists in their career might experience a few eureka moments - the surprise of a new insight leading to a paradigm shift. However, surprises are often serendipitous in my experience - for example our discovery of the late origin of the germ line in mammals in 1983 (thus ending the Weissman theory of continuity of the germ line in mammals) and the process of deprogramming of the sperm and egg genomes in the first week of development in 1987 (thus ending the dogma that the sperm and egg are the tabula rasa beginning of development and opening the field of stem cell regenerative medicine). The problem with being the author of such surprising discoveries is that they are not believed by others in the field (not for around ten years for both of the discoveries mentioned above). It seems to me a paradigm shift must involve serendipity because you cannot be looking for something that has not yet been thought of or has even been excluded by the current scientific dogma. It has to find you.

Another factor leading to new discoveries is change of field. My main discoveries were partly due to a change of field which introduced my 10 years of experience of molecular biology in microorganisms into early mammalian development (thus originating the field of molecular embryology). Unexpected, surprising discoveries also depend on the need for the scientist to be committed to trying to disprove her hypothesis (as defined by Karl Popper). New discoveries require attention (almost attraction) to things that don't fit - an obsession with the anomalies normally dismissed by many scientists with a 'pet hypothesis' as 'experimental artifacts'.

So what may seen as genius in new discoveries may be, in many cases, a combination of factors. First the characteristics favouring scientific endeavour – wonder, curiosity, passion, honesty, observation, discipline, thoroughness, perseverance, joy in experiments, open-mindedness, flexibility and love of conceptual elegance. Add to these excessive doubt, attraction to things that don't fit, possibly ignorance of the field and its dogmas, and also, in some cases, careless errors in setting up the experiment (as happened in my case with an omission in a reaction mix that revealed the surprising first case of single cell molecular biology). Another factor influencing new surprising discoveries is the freedom given to young scientists to follow and develop their interests. For some reason I was always given complete freedom in my research by a succession of brilliant bosses – Bill Hayes (microbial genetics and slime mould aggregation), Anne McLaren (early mammalian development), Roland Levinsky (my own molecular embryology unit). In addition, I was lucky to be developing my science career in the days of support for academic research (now called, pejoratively, blue-skies research). Sadly, from the 70's onwards, funding was directed away from academic research to applied research (directed towards a desired outcome).

What of real genius? Einstein (whose theory of relativity linked matter and energy, $E = mc^2$), Galileo (telescopic astronomy), Copernicus, Descartes, Newton, Curie, Louis Pasteur, Darwin (evolution by natural selection) and more recently Jung, Franklin, McClintoch, Hawking, Feynman, Watson. You will have a list of your own perhaps?

References

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Temporal and regional changes in DNA methylation in the embryonic, extraembryonic and germ cell lineages during mouse embryo development.
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Saving the Tasmanian Devil

The Tasmanian Devil suffers from a rare form of facial cancer that is contagious from one animal to another. This is highly unusual as the cancer cells of one animal should be seen as foreign in another animal and rejected by its immune system. Immune rejection is the reason why cancer is mercifully not normally contagious. People have previously thought that the facial cancer cells evaded detection in the Tasmanian Devil because the animals had low genetic diversity especially in the genes of the major histocompatibility complex (MHC) which produce proteins located on the surface of cells and direct the immune system to detect threats such as viruses or tumours. But this is not the case for the contagious facial cancer in the Tasmanian Devil which, in fact, has evolved a way of escaping immune recognition. Since the contagious cancer is always lethal the Tasmanian Devil is facing extinction.

In a collaborative effort between researchers at a number of universities in Cambridge and Australia, Siddle and Kaufman and coworkers have investigated the mechanism by which the cancer cells escape immune recognition and elimination. They have shown that the cancer has evolved to suppress cell surface antigens that are required for immune response. The suppression is not due to mutation but modifications super-imposed upon the genes (epigenetic modification) essential to the MHC antigen-processing pathway, so as to render the genes inactive (unable to make corresponding MHC proteins). They were also able to restore MHC class I molecules on the surface of cancer cells *in vitro* by removing the DNA modifications that were suppressing the gene activity. The authors propose that the use of MHC-positive or epigenetically modified cancer cells may provide a vaccine to protect the animals from lethal facial cancers. A similar contagious cancer has been known for some time to occur in dogs - canine transmissible venereal tumour – which however is rarely fatal. This work is highly significant in terms of the possible evolution of other contagious cancers in other species and the development of measures to control and/or eliminate them if that were to happen.

Reference

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***Marilyn Monk** is UCL Emeritus Professor of Molecular Embryology at the Institute of Child Health, University College London, and Honorary Professor at Melbourne and Monash Universities, researching gene expression and its regulation in development and cancer. She is also an Alexander Technique Teacher and Psychosynthesis Counsellor.*