Recent Developments in Science and Medicine

Marilyn Monk

Sexy goats in hats

Pheromones are chemicals given off (secreted or excreted) as a form of communication throughout all forms of life. Specific pheromones influence physiology and behaviour (e.g., territorial boundaries, alarm, food trail, sex, etc.) in members of the same species. Most sex pheromones are produced by females. However, recently it has been shown in sheep and goats that males produce scents that stimulate fertility and induce ovulation in female goats. Murata and colleagues (Department of Animal Resource Sciences, University of Tokyo, Japan) have identified the specific scent produced by male goats that brings on sexual maturity in females. Male goat pheromones are generally synthesised in the animal's head skin so the researchers fitted male goats with special hats that collected all the scents given off over a period of a week. The pheromones were recovered from the hats and analysed by gas chromatography-gas spectrometry. They identified a single molecule, 4-ethyloctanal, amongst all the male goat pheromones that activated the neural pathway that regulates reproduction in females. The purified chemical has a distinctive orangey-floral odour and has not been previously found in nature. A similar effect is known in mice and rats where the presence of males can speed up puberty in females. The research could be used to develop new, more-natural, ways to improve the efficiency of breeding. The work is now being extended to other important livestock animals, such as sheep and cows.

Reference

Murata K, Tamogami S, Itou M, Ohkubo Y, Wakabayashi Y, Watanabe H, Okamura H, Takeuchi Y, Mori Y.
Identification of an olfactory signal molecule that activates the central regulator of reproduction in goats.
Curr Biol. 24:681-686 (2014)

Evolution within a single gene explains polymorphic mimicry in butterflies

Mimicry of appearance, behaviour, sound, scent or location, is selected by evolution due to the protection from predation it affords to a species. A recent case of mimicry is of particular interest because it is sex-limited and polymorphic. In the swallowtail butterfly genus, Papilio polytes, only the female mimics the wing pattern of other species of butterflies that are toxic and thus avoided by their predators. The mimicry in the female is polymorphic in that females of this one species mimic the colour patterns of several toxic species to avoid predation. Surprisingly, the entire wing pattern phenotype, although variable, has been shown to be controlled by a single evolutionarily-conserved gene which also controls aspects of sexual differentiation in most animals (thus explaining the sex-limited mimicry to the female butterfly). Kunte and coworkers (Department of Ecology and Evolution, University of Chicago, USA) used an integrative approach combining genetic and association mapping, transcriptome and genome sequencing, and gene expression analyses, to show that a single gene, doublesex, controls supergene mimicry in Papilio polytes. The different mimicry types are explained by multiple DNA sequence variation within this single gene to switch the entire wing pattern. This explanation of the nature of a mimicry supergene at a functional level is in contrast to the long-held view that supergenes are likely to be controlled by a tightly linked cluster of loci.

Reference

Kunte K, Zhang W, Tenger-Trolander A, Palmer DH, Martin A, Reed RD, Mullen SP, Kronforst MR.
Doublesex is a mimicry supergene.
Nature 507:229-232 (2014)

An elephant never forgets

In addition to sight and smell, animals can normally distinguish the magnitude of threat by the sounds made by their different predators. Human predators are an interesting example as some humans are more of a threat to animals than others. Traditionally elephants have been hunted by the Maasai people and especially in times when there is a need to clear pasture for grazing livestock. McComb and co-workers (Mammal Vocal Communication and Cognition Research, University of Sussex, Brighton, UK) have recently used controlled playback experiments to show that free-ranging African elephants (Loxodonta africana) in Amboseli National Park, Kenya, exhibit different behaviours in response to hearing the voices of two Kenyan ethnic groups - the Maasai, who hunt the elephants, or the Kamba, a crop-farming group that rarely has violent encounters with elephants.

On hearing playback of voices of the Maasai, but not the Kamba, the elephants exhibit defensive bunching and investigative smelling. The researchers also showed that the animals responded differently according to the age and sex of the Maasai voice they were listening to. They were much more alarmed by an adult Maasai male voice than by the voices of Maasai women or Maasai boys. The ability to discriminate different levels of threat according to human voice is probably culturally inherited (taught to offspring by parents or by elders in the herd) as herds led by old matriarchs never responded to the voices of boys whereas those led by younger matriarchs did react to the boys' voices half the time

This intelligence in animals discriminating the magnitude of threat by various means, including voice recognition, reminds us that sophisticated conscious awareness is not solely a human trait. It is interesting that laboratory mice are more afraid of male researchers than of female researchers (Sorge et al, 2014). This may possibly be due to scent. However, I have also observed that mice and other animals (e.g., our cats, dogs and horses) discriminate something about the relative safety of a human being at an individual level as well. A wonderful example of animals that seem to have no fear of human predators in general is experienced with a visit to the Galapagos.

References

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Elephants can determine ethnicity, gender, and age from acoustic cues in human voices.
Proc Natl Acad Sci U S A.111:5433-5438 (2014)

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Olfactory exposure to males, including men, causes stress and related analgesia in rodents.
Nat Methods 11:629-632 (2014)

Biomarkers predicting Alzheimer's disease

Research is moving further away from genes and DNA (and the central dogma) and finally acknowledging that our interface with our environment, and the functioning of our cells and tissues, is much more closely linked to cellular metabolism – the 3000 interconnected biochemical reactions within each cell that continually flux and balance according to requirement for function. Hence, we hear more and more of the discovery of biomarkers (observed as the up-regulation or down-regulation of different metabolites) that indicate an altered place of balance of the metabolome. This takes me happily right back to my student days where it was a requirement to have the Boehringer chart of metabolic pathways pinned to the door of the loo. My later research was also often more geared towards biochemistry - for example, the development of microassays to detect activities of multiple enzymes at the sensitivity of the single cell, and the first application of such microassays to preimplantation diagnosis of genetic disease (Benson & Monk, Mammalian Development Unit, University College, London).

Now biomarkers have been identified that detect the early onset of Alzeimer's disease. A large collaborative effort in USA headed by Mapstone, Federoff and co-workers (Universities of Georgetown Washington, Rochester New York and Irvine California) followed a group of 525 cognitively normal older (over 70) adults and discovered ten lipids (normally present in cell membranes) from their peripheral blood that predicted cognitive impairment or Alzheimer's disease within a 2 to 3 year timeframe with over 90 per cent accuracy. In this study, 28 of the 525 participants developed symptoms similar to those of Alzheimer's disease (larger studies will be needed in the future). Alzeimer's disease is a devastating condition affecting 35 million people world-wide and numbers are expected to increase to 150 million by 2050. Current biomarkers for early dementia - such as cerebrospinal fluid testing and MRI (magnetic resonance imaging) are invasive, time-consuming and expensive. There is still no known cure for Alzeimer's disease but it is hoped that biomarkers enabling early detection might lead to effective intervention to delay or ameliorate ongoing symptoms, or even prevent the onset of debilitating disease. A problem arises in that people being tested in the future by this easy blood test might not want to know the result - especially if there is currently no treatment or cure.

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Plasma phospholipids identify antecedent memory impairment in older adults.
Nat Med. 20:415-418 (2014)

The beauty of maths

Many people who have studied mathematics will appreciate the feeling of beauty – even of perfection – in the elegance of evolving a mathematical equation to its end and then the immense satisfaction in the writing of QED. Some compare the experience with that of appreciation of the finest art. Zeki and colleagues (Wellcome Laboratory of Neurobiology, University College London; Department of Physics, Imperial College London; School of Mathematics, University of Edinburgh) have established a new field of neurobiology - neuroaesthetics – the study of the relationship of visual art to the functioning of the visual brain. They asked - could the intellectual appreciation of abstract mathematics as beauty be involving the same brain function as the more emotional appreciation of the beauty of art or music?

Previous brain imaging studies have shown that the experience of visual and musical beauty is associated with activity in a specific part of the emotional brain called the medial orbito-frontal cortex. The researchers employed functional magnetic resonance imaging (fMRI) to observe the activity in brains of 15 mathematicians as they viewed mathematical formulae which they had individually rated as beautiful, indifferent or ugly. They found that the same brain area associated with emotional reactions to beauty activates when mathematicians view especially pleasing mathematical formulae. Presumably, only people who understand the meaning behind the mathematical formulae will find them beautiful and, indeed, the brains of a control group of non-mathematicians showed a lesser emotional response. On the other hand, people with no musical or artistic training can still appreciate great musical and artistic works. What is beauty then? Beauty is not necessarily something that makes one happy. Maybe happy or sad it is an experience that tugs at the heart strings.

Reference

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The experience of mathematical beauty and its neural correlates.
Front Hum Neurosci. 8:68 (2014)

The interconnectedness of ecosystems

The study of ecosystems is the study of interconnectedness. Ecosystems are complex and variable. An intercommunicating network of plants, bacteria, moulds, insects, parasites, trees, forests, small animals, large animals, herbivores and carnivores, and of course, humans. Everything is connected to everything else (c.f., the interconnected balance of 3000 metabolic pathways in each cell that I talked about above). Each part, and therefore the whole, is affected by geology, climate, climate change, natural disasters and human interference. How are ecosystems regulated?

There are some who favour top down control – populations of carnivores regulate the whole system. Others favour bottom-up control – the abundance and quality of the photosynthesising plants feeding the ecosystem. Most people have a tendency to favour top down control and to focus on what is happening to the survival and geographic ranges of the large carnivores. Ripple, Wirsing and colleagues (Department of Forest Ecosystems and Society, Oregon State University, USA) report on 31 large carnivores on earth and the effects of removing them from their ecosystems or introducing them to new ecosystems. They show that large carnivores have substantial effects on the structure and function of their ecosystems. They affect the well-being and survival of all other wildlife in the ecosystem including humans, e.g., via possible crop damage.

This complex subject is reviewed in an editorial in *Nature* in March this year - 'An elegant chaos' - with particular reference to an article by Emma Marris on the role of predators in shaping the ecosystem, viz., wolves in Yellowstone National Park and dingoes in Australia. Wolves were exterminated in Yellowstone in the 1920s and restored in the 1990s after which the willows flourished. It was thought that the re-introduction of the wolves frightened the elks, which prevented them from grazing on the willow trees. But it became clear that there were many other factors affecting the size of the elk population – including beaver dams, grizzly bears, past history and the weather. So the regulation of the ecosystem is not only bottom up or top down but 'middle-out' as well. In fact, with interconnectedness everything affects everything else and a unified theory of everything is required to understand ecosystems and to make predictions about their future. The aim of these studies of course is to protect the complexity and variability of ecosystems and to care for conservation and prevent extinctions. The very beauty of ecosytems is their constant flux and play with the environment.

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Science 343:1241484 (2014)

Emma Marris
Rethinking predators: Legend of the wolf.
Nature 507:158–160 (2014)

Nature editorial
An elegant chaos.
Nature 507:139–140 (2014)

Cancer you don't know you have

London scientist Mel Greaves (Centre for Evolution and Cancer, The Institute of Cancer Research, Sutton, Surrey, UK) asks, in an editorial published in *Nature*, 'Does everyone develop covert cancer?' Covert cancer is a hidden or subclinical cancer that we do not know about ourselves but which might be uncovered by screening. Certainly, we have been alerted recently to the problem that many tests to detect early onset cancer – cervical screening, breast screening, PSA tests for prostate cancer – have a high risk of alerting doctors to cancers that might never go on to threaten life. Wide spread breast screening has made very little difference to the numbers of women who die of breast cancer and, moreover, leads to invasive treatments on millions of women that might have been unnecessary. Problems with prostate glands are found during autopsy in a majority of men in their late 70s and 80s yet they did not die of prostate cancer. In fact, the number of many different types of cancer inadvertently discovered at autopsy far exceeds the number known to cause death in the population as whole. From these data one can calculate the specific rates at which different covert cancers develop to malignant cancer – from less than one per cent to say 80 per cent depending on the specific cancer. Early detection is important when intervention is minimally invasive such as removal of skin cancers and polyps. More invasive treatment that might not be necessary is problematical. On the other hand, medical teams that fail to treat may face litigation.

Now that we live for so much longer, one in three of us eventually die of cancer. In addition, it is highly likely that we all develop one or more cancers in our life time that we do not know about. It is important to distinguish between a tumour and a cancer. A tumour is an abnormal growth of cells anywhere in the body to form a lump which may stay the same size, grow very slowly, or just be there for a while and disappear. A cancer is more aggressive in that mutated cells that grow faster are constantly selected and cells which develop the ability to migrate and colonise other tissues (metastasis) enable the cancer to spread to other parts of the body (malignancy). Thus, cancer cells may arise by accumulation of successive mutations from within a tumour that has been present for years or even decades.

Mutation is a fact of life and we accumulate more mutations in time as we grow older. Our cells are undergoing millions of cell divisions every day and, with a spontaneous mutation rate of say one in a million divisions, mutations are inevitable. Greaves points out that given our risky life style it is perhaps more surprising that our rate of death from cancer in 80 to 90 years of life is only one in three. What is needed is clarity about the likelihood that a covert cancer will go on to a malignancy as well as foreknowledge of the invasiveness and effectiveness of early intervention. With this information it may be possible in the future to weigh up the relative merits of the different courses of action.

Reference
Mel Greaves
Does everyone develop covert cancer?
Nature Reviews Cancer 14:209–210 (2014)

Your nose can distinguish a trillion smells

If only we had the animal awareness of our ancestors we could go for a run in the park with our dog and maybe find all the smells just as exciting as our dog finds them. We tend to think that we do not naturally have such a refined sense of smell. Until recently science has considered that humans can discriminate around 10,000 different smells but in fact this is an underestimate of our abilities. Bushdid, Keller, and coworkers (Laboratory of Neurogenetics and Behaviour, The Rockefeller University, New York) have subjected 26 volunteers to scent mixtures of 10, 20 or 30 ingredients from a total of 128 odours. They calculated that humans can discriminate up to a trillion different olfactory stimuli. The human nose has 400 types of scent receptors and specific receptors detect different molecular components in a smell. The challenge for research now is to understand how the receptors in the nose inform the brain so that we are able to discriminate different smells. Interestingly the discrimination of the sense of smell far exceeds that of the other senses of sight (colours) and sound (tones).

Reference
Bushdid C, Magnasco MO, Vosshall LB, Keller A.
Humans can discriminate more than 1 trillion olfactory stimuli.
Science 343:1370-1372 (2014)

Diagnosing disease with the epigenome

The sequencing of the entire human genome held out much promise. If we could know the sequence of all our genes then we could diagnose which genes were altered to cause specific diseases. And indeed this is true for a certain number of diseases associated with alteration of a single gene, such as Duchenne muscular dystrophy, cystic fibrosis or thalassaemia (there are a few thousand monogenic diseases known). But in other cases a disease might be associated with changes in a number of genes. So researchers now carry out genome-wide association studies (GWAS) to identify the genes involved in multigenic disorders. Nevertheless, sometimes definitive information is elusive. Now we know it is not just about the genes themselves but the programming of the genes which determines which of them are active and which are inactive in certain cells in certain tissues. In computer terminology, we can think of the genes as the hardware and the programming as the software. The programming works by modifications superimposed upon the genes – epigenetics. One of the most important programming modification is methylation of one of the DNA bases - cytosine - in the regulatory DNA sequence of a gene. So now researchers are carrying out epigenome-wide association studies (EWAS) to see which genes are methylated in certain conditions. The research presents a number of challenges. Are the changes observed a cause or consequence of the disease? Is the mixture of different cells in the blood sample likely to give the same result as cells from an organ or tissue which is specifically defective in a particular disease.

Nevertheless, inroads are being made. These studies involve collaboration between many scientists distributed over a large number of universities and research institutes. For example, universities in the UK, Germany, France, Sweden and Canada, have carried out epigenome-wide analysis of the pattern of methylation of blood DNA associated with obesity (body mass index) on an initial cohort of 479 European patients. Subsequently, the results were checked on 339 patients of a different cohort, and checked again on 1789 white patients of European origin from yet another cohort. Methylation levels at identified sites in blood also showed an association with body mass index (BMI) in DNA from adipose tissue but not from skin. Increased methylation at a specific locus (HIF3A) in blood cells and adipose tissue suggest alterations in hypoxia (low oxygen) inducible transcription factor pathways may play an important role in obesity. Obesity is a major health problem. Clearly lifestyle and environment play a role as well as genes and their programming.

Reference
Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aïssi D, Wahl S, Meduri E, Morange PE, Gagnon F, Grallert H, Waldenberger M, Peters A, Erdmann J, Hengstenberg C, Cambien F, Goodall AH, Ouwehand WH, Schunkert H, Thompson JR, Spector TD, Gieger C, Trégouët DA, Deloukas P, Samani NJ.
DNA methylation and body-mass index: a genome-wide analysis.
Lancet 383:1990-1998 (2014)

Transgenerational inheritance of stress

The previous article considered studies on differences in whole genome methylation correlating with specific disease states. Another recent paper explores a different form of epigenetic modification regulating specific gene expression – namely the inheritance of small regulatory RNAs, or microRNAs. RNA (ribonucleic acid) is a related molecule to DNA (deoxyribose nucleic acid), RNA may serve a number of functions. Messenger RNA carries the code of the DNA from the nucleus to the cell cytoplasm to specify specific proteins coded by specific genes. Regulatory, or non- coding microRNAs work in the other direction, i.e., to recognise and regulate activity of specific DNA sequences. An interesting recent paper has implicated the inheritance of certain microRNAs through the germ line (eggs or sperm) as the basis of inheritance of stress. Stressing parents can cause their offspring to be stressed even though the offspring were not submitted to the stressful conditions. It has been known for some time in humans that trauma is inherited but in many cases this could be due to an effect of parenting - so called cultural or social inheritance.

Now we know that inherited trauma can also be a consequence of direct inheritance via sperm. Gapp, Mansuy and co-workers (Neuroscience Center Zürich, University of Zürich) found altered microRNA expression in the sperm of stressed male mice and altered behavioural and metabolic responses in their progeny for at least two generations. Injection of the altered RNAs, obtained from sperm, into eggs also transmitted stress behaviour to offspring. The stressed male offspring showed depressive behaviours and their sperm also exhibits abnormally high expression of five microRNAs, one of which, miR-375, has previously been linked to stress and alteration of sugar metabolism. These changes and the abnormal levels of the microRNAs in blood and hippocampus were inherited through two generations. It is not known how stress alters the microRNAs in sperm and, intriguingly, the continued transmission through generations is not associated with the continued presence of the microRNAs in sperm so it must be taken over by some, as yet unknown, epigenetic mechanism. The researchers are now looking at levels of these microRNAs in stressed humans and their children.

Reference
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Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice.
Nat Neurosci. 17:667-669 (2014)

Amoebae races - place your bets

An article in *Nature* in May prompts me to write about my favourite organism - the slime mould amoeba, *Dictyostelium discoideum*. The article ' The Game is On' is about a race set up in Boston Massachusetts to see who can train their amoebae to move the fastest through a 800 mm silicon maze towards a bacterial food source. The prize was US$5,000 and an appearance at a *Dictyostelium* conference in Germany this August. A Dutch team took first place, closely followed by a team from the United Kingdom, and then by a team of Germans. The idea of the competition is to foster interest in how cells move towards a food source. In fact, most cells will move towards something nourishing and move away from something toxic or poisonous. And this is the least interesting thing about *Dictyostelium*. The wondrous thing about *Dictyostelium* is that it has two levels of existence.

Individual free living amoebae enjoy chomping on decaying vegetation until the food runs out. The onset of starvation is a signal for the amoebae in a particular territory to aggregate to form a multicellular structure. To do this, certain individual amoebae pulse out a chemical signal of cyclic AMP which diffuses into the surrounding area. Other amoebae within range of the diffusing cAMP respond by making a movement step towards the source amoeba and also they themselves emit a signal of cAMP. Thus the signal is relayed out in waves as bands of amobae move in in waves. Sometimes hints of this process could be seen as circles of amoebae on a surface of a plate in the laboratory but the patterns were elusive.

I used to take plates home and get up at intervals throughout the night to try to catch the amoebae aggregating so as to work out how they did it. But with no success. And then one night, exhausted , I threw the plates into the fridge (I might normally have left them on the dining room table). The next morning there were perfect waves of aggregating amoebae. The fridge was old and only reached 8°C and somehow this temperature cut between the movement and signalling in such a way that perfect wave patterns were formed. (The published paper says plates were incubated at 8°C!) Together with my student at the time, Fernanda, we were able to analyse the bands of moving and stationary amoebae by time lapse cinema photography and work out all the parameters of aggregation – the signal periodicity, the signal velocity, the duration of movement step, the distance covered, the refractory period, and so on.

Aggregating amoebae form wonderful spirals that look like galaxies. When all the amoebae have gathered they pile up and the heap falls over and forms a slug. The slug can move centimetres whereas individual amoebae only move micrometres. So, the purpose of the slug is to move towards the heat and the light (the organiser tip of the slug is thermotactic and phototactic) - in other words towards the soil surface. Here, with evaporation of ammonia, the slug transforms into an elegant fruiting body - a head of spores held aloft by a cellulose stalk. During their time in the slug, the amoebae have differentiated into different cell types. A third of the amoebae sacrifice their lives to form the stalk of the fruiting body. From here the spores can be picked up by a passing insect and disseminated to find another feeding ground.

So, back to the races. I had tremendous fun organising slug races in the dark room of the Department of Molecular Biology, Kings Buildings, Edinburgh, in the early 70s. Slugs were chosen by the race goers, lined up, money laid down, a light source set up at a suitable distance, and 'they're off'.

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The game is on
Nature 509,134 (2014)

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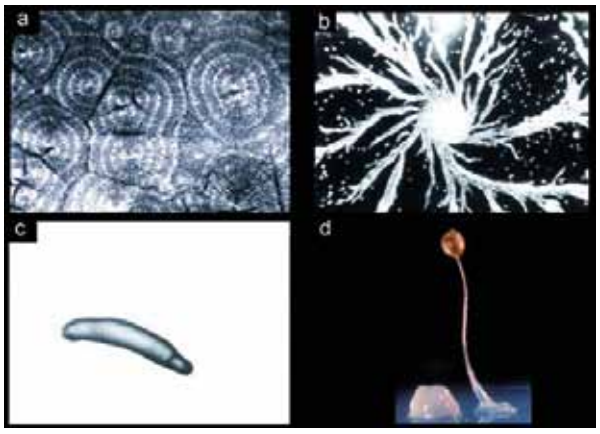

Marilyn Monk *is UCL Emeritus Professor of Molecular Embryology at the Institute of Child Health, University College London, and Honorary Professor at Melbourne and Monash Universities, researching gene expression and its regulation in development and cancer. She is also an Alexander Technique Teacher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