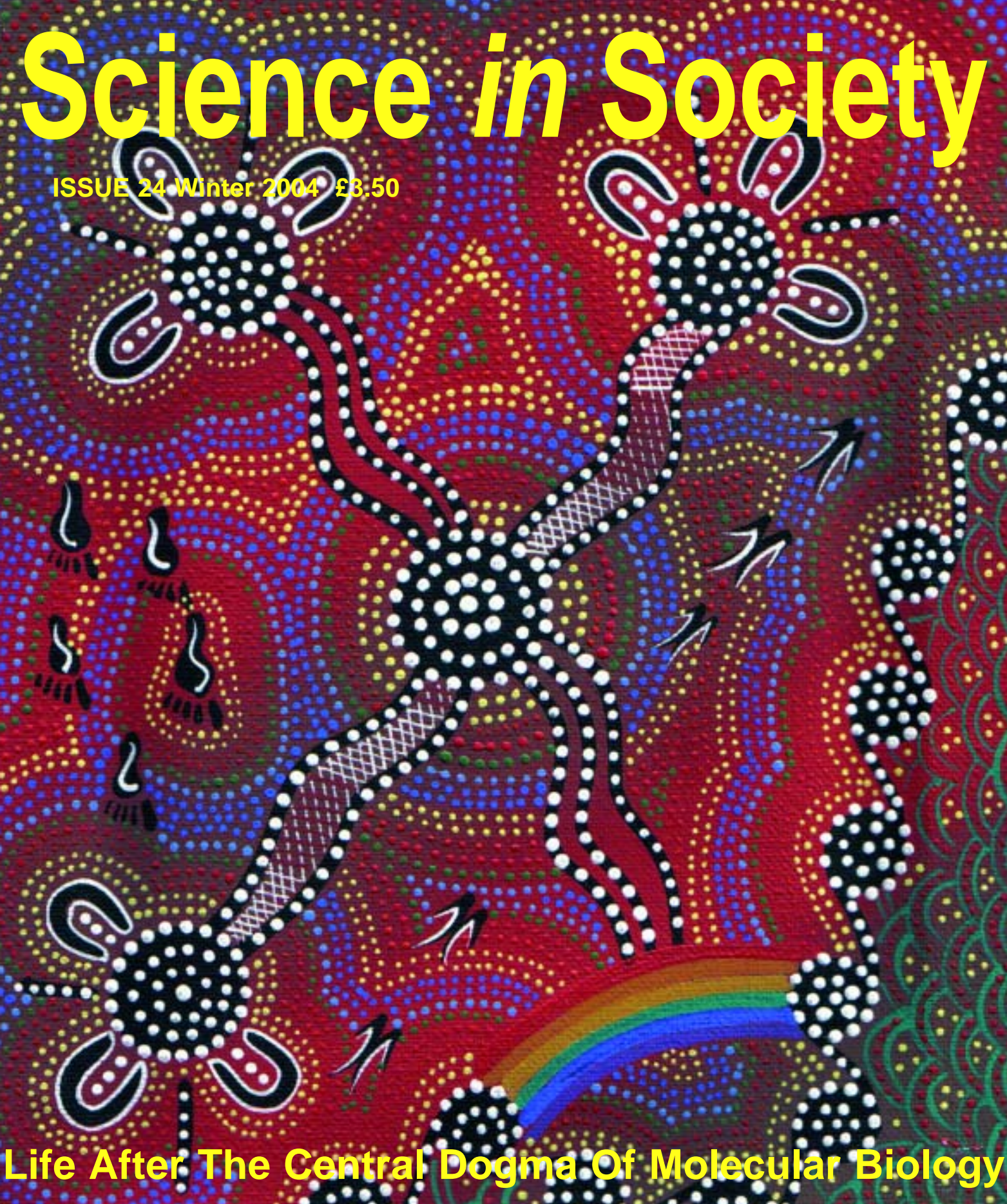


Science *in* Society

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Life After The Central Dogma Of Molecular Biology

Water & The Tao Of Cell Biology - What Text Books Won't Tell You
Sustainable Agriculture Needed To Feed The World Under Climate Change

Mobile Phones Damage Brain Cells - Biophysics of EMF Sensitivity
Rice Rich In Iron gets Arsenic - Freeing the World From GM



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From the Editor

Death of the Central Dogma and beyond

The biotech industry was launched on Francis Crick's infamous 'Central Dogma of molecular biology', the scientific myth that organisms are hardwired in their genes, and hence, by moving genes across species separated by billions of years of evolution, new 'genetically modified' organisms could be created to serve our every need.

The Central Dogma has been thoroughly exploded by scientific findings accumulating since the mid-1970s, and especially so after the human and other genomes have been sequenced (see *Living with the Fluid Genome*, by Mae-Wan Ho www.i-sis.org.uk).

We bring you the latest surprises that tell you why our health and environmental policies based on genetic engineering and genomics are misguided; and more importantly, why the new genetics demands a thoroughly ecological approach to life.



"GM crops are a dead end, invest in non-GM sustainable agriculture right now"

The Independent Science Panel (ISP) (see *SiS* 18) took its campaign for a GM-free sustainable world to the European Parliament on 20th October 2004. One hundred and twenty registered for the special briefing including 27 who crossed the channel with the scientists from the UK. The event made a big impression and the participants could not stop congratulating us afterwards. We thank all our sponsors and supporters for making it such a success. *Cordis News*, the official EU news service for science and technology reported the event the very next day with the title "Politicians, professors and protestors target sustainable non-GM agriculture". Further media coverage was still coming in five days later.

The ISP message is crucial as GM battles are raging across the world. The high point of the briefing was the talk by Sue Edwards, Director of the Institute for Sustainable Development, who helped convince the Ethiopian government to adopt an organic composting, water and soil conservation package as its main strategy for combating land degradation and poverty throughout the country (see *SiS* 23). It brought home the proven successes of low-input, health enhancing agricultural practices that should be adopted all over the world.

Sustainable agriculture is particularly important under climate change when oil and water - on which industrial agriculture, and even more so, GM agriculture are heavily dependent - are both running out. Industrial agriculture uses up to seven times the energy per tonne of food than organic agriculture; it also turns organic soil, which is a carbon sink, into a carbon source, and generates other greenhouse gases that exacerbate global warming. In order to feed the world, we must invest in sustainable, non-GM agriculture across the globe right now, which will also ameliorate the worst consequences of climate change.

At the same time, important changes have to be made in international agencies and institutions, which have hitherto supported the dominant model of industrial agriculture as well as policies that work against poor countries, where farmers are also desperately in need of secure land tenure.

Biological effects of EMFs still in search of a mechanism

More and more biological effects of electromagnetic fields are documented at weaker and weaker field intensities, suggesting that the current exposure standards - which are aimed at preventing outright heating of tissues - may be up to 10 million fold too high, if we are to really protect the public. Researchers are finding long-lasting brain damage in rats exposed to mobile phones, as well as a range of health problems among people living near the mobile phone masts.

Still, the regulators profess themselves powerless to lower the exposure limits because of the lack of plausible mechanisms - within conventional mainstream science - that could explain how fields with such minute energies could have any biological effects. Leukaemia, DNA damage in brain cells and other electromagnetic field effects cannot be explained unless scientists communicate and collaborate across the disciplines, which they are currently unable to do, partly due to the lack of interdisciplinary education, partly due to existing funding structures in research and the general culture of mainstream science that overwhelmingly discriminates against innovative people and ideas (see also *SiS* 17). Will our government take the radical steps needed in scientific research funding and in science education to improve both the quality of our science and its ability to protect the public?

Water, the medium of life

Entire biochemistry and cell biology textbooks will have to be rewritten to put water at the centre of living activities. It is indeed water inside cells and in the extracellular matrix that's stage-managing the continuing drama of life. Enjoy and marvel!



Nichts geht mehr by Helga Kreuzritter, Germany

Death of the Central Dogma

Dr. Mae-Wan Ho
reports

It is amazing how much scientific and religious fundamentalism have in common. The late Francis Crick won the Nobel Prize jointly with James Watson and Maurice Wilkins for working out the structure of DNA; and rather like the new 'Potentate' of biology, issued the 'Central Dogma' to the faithful, which decreed that genetic information flows linearly from DNA to RNA to protein, and never in reverse. That was just another way of saying that organisms are hardwired in their genetic makeup, and that the environment has little, if any, influence on the structure and function of the genes.

The Central Dogma goes hand in glove with the other dogma of biology, the neo-Darwinian theory of evolution by natural selection, which says that the genetic material mutates at random, and individuals that happen to have good genes leave more offspring, just as individuals with bad genes are weeded out. The neo-Darwinian theory is beloved of the *status quo*, because it endows the rich and powerful with a certain mystique, as those who have won the race in the struggle for survival of the fittest, and of being in possession of good genes (= good breeding); while the poor and dispossessed have only their bad genes to blame.

Since the mid-1970s, if not before, molecular geneticists studying the genetic material have been turning up evidence that increasingly contradicts the Central Dogma. There is an immense amount of necessary cross talk between genes and the environment in the life of the organism, which not only changes the function of the genes but also the structure of the genes and the genomes. By the early 1980s, the new genetics of the "fluid genome" had emerged.

But apart from a few heretics like Barry Commoner and myself, no one has dared to say a word directly against the Central Dogma or the neo-Darwinian theory of evolution.

Things may have changed within the

past two years, thanks to the good sense and good management of the public gene-sequencing consortium to insist on depositing gene sequences in a single public database, freely available to all researchers.

This database is not much use for business and drug discovery; that much is clear, as one 'bioinformatics' company after another that tried to hoard the data went out of business. But, collected in one freely accessible central database, it is very good for research that exposes the poverty of the ideology of genetic determinism that led to the creation of the database in the first place.

The evidence against the Central Dogma has piled up to such an extent that rumblings of "challenging the dogma" and "a new theory is needed to replace the central dogma" can even be heard in the mainstream scientific journals. Though Dr. Ewan Birney, who gave the Royal Society's inaugural Francis Crick Lecture in December 2003, still paid elaborate homage to the Central Dogma.

What are the latest surprises that the fluid and flexible genome has in store? One area is the importance and pervasiveness of epigenetics, specifically, chemical markings on the DNA and on proteins binding to the DNA in the chromosomes. These chemical markings identify which bits of the genetic text are actually read, and are overwhelmingly determined by experience. In an earlier issue (*SiS* 20), we showed that the mother's diet and stress can affect patterns of gene expression in the embryo and foetus, which in turn determine the individuals' health prospects much later in life.

Now, researchers are finding genes that are marked for life in rat pups, strictly by how their mothers care for them during their first week of life after birth (see "Caring mothers reduce response to stress for life", this series). It leaves one in no doubt that the environment is giving the instruction on

which genes to turn on.

Only a few years ago, people were referring to the 98% or more of the genome that doesn't code for proteins as "junk DNA". Not any more. The genome has a definite 'architecture' that holds up beneath the fluidity. There is a high degree of non-randomness in the parts of the genome that undergo change. While some parts are hypermutable, certain families of sequences are 'homogenized' to be nearly identical (see "How to keep in concert", this series), while still others are 'ultraconservative' in that they have remained absolutely unchanged in hundreds of millions of years of evolution ("Are ultraconserved elements indispensable?" this series). And when cells get into a tight corner metabolically speaking, there may even be genes that mutate to get them out of it ("To mutate or not to mutate?", this series).

Most of all, there is a big treasure trove within the apparent junkyard of the genome. Many sequences that don't code for proteins are involved in regulating development and gene expression. Many of the surprises are associated with findings that indicate most of the action is not in proteins, but in the numerous species of RNA 'interfering' at all levels of the 'readout' of genetic information: with the DNA, with other RNA species, and with proteins (see "Subverting the genetic text", this series).

All of this goes against the very grain of the Central Dogma that posits linear, mechanistic control. Instead, layer upon layer of chaotic complexity are coordinated, it seems, by mutual agreement, in an incredibly elaborate, exquisite dance of life that dances itself freely and spontaneously into being.

It is not so much that we need a new theory to replace the central dogma; it is more important than that. We need a new way of knowing and being organisms that will prevent us from mistaking organisms for instruments and machines. That's the real challenge.

Are Ultra-conserved Elements Indispensable?

Geneticists have identified elements in the genome that are 'ultra-conserved', and thought that they must be indispensable for survival. Not so. **Dr. Mae-Wan Ho** reports

The 'molecular clock' of mutational changes

Until now, *most* geneticists have believed that the DNA in the genome is subject to random mutations, *most* of which are neutral - neither good nor bad for the organism - so that the result is a slow and steady change in DNA sequences in the genome in the course of evolution. This is the basis of the 'molecular clock' hypothesis, which enables one to estimate, from the changes in DNA, the time in the past at which certain evolutionary events happened. For example, when it was that the first human immune deficiency virus (HIV-1) split off from the monkey virus (SIV), or, much, much further back in evolution, when the line that led to the human species split off from the one that led to the chimpanzee.

The molecular clock is known not to be perfect, because different genes tend to change at different rates, though the rates were not that dissimilar. So it was always assumed that, averaged over the whole genome, the molecular clock would give relatively accurate results; particularly, as it had seemed, until quite recently, the genome was full of "junk DNA" of unknown function.

"Ultra-conservative elements"

Many surprises lay in store as genome sequences accumulated, and fortunately, deposited into one public database, so useful comparisons could be made. It turns out that not only are there vast hidden treasures among the "junk DNA", but there is evidence of highly non-random changes among different stretches of the DNA, some of which change in concert, some change at random, and others almost not at all.

There are 481 segments in the human genome longer than 200 bp that are 100% identical with rat and mouse genomes. Nearly all are conserved as well in the chicken (467/481) and dog (477/481) genomes, with an average of 95.7% and 99.2% identity, respectively. Many are also significantly conserved in fish (324/481 at an average of 76.8% identity).

Very few of these elements could be traced back to jelly fish, *Drosophila* or the nematode worm.

These "ultra-conserved" elements are widely distributed in the genome, occurring on all chromosomes with the exception of the Y chromosome and chromosome 21. They most often overlap exons in genes involved in RNA processing or occur in their introns; or near genes involved in regulation of transcription and development.

Of the 481 ultra-conserved elements, 111 overlap the mRNA of a known human protein coding gene, including the UTR (untranslated region) and are partly exonic (belonging to protein coding sequences); 256 show no match to expressed mRNA and are therefore non-exonic (non-protein coding); while the remaining 114 are possibly exonic. One hundred of the non-exonic elements are located in introns (non-coding intervening sequences) of known genes and the rest are intergenic (between genes). The non-exonic elements, both intronic and intergenic, tend to congregate in clusters near transcription factors and developmental genes, whereas the exonic and possibly exonic elements are more randomly distributed along the chromosomes.

There are 93 known genes that overlap with exonic ultra-conserved elements; these are called type 1 genes. The 255 genes that are near the non-exonic elements are type II genes. Type I genes tend to be RNA binding or involved in the regulation of splicing. In contrast, type II genes are involved in the regulation of transcription and DNA binding, and are enriched for DNA binding motifs such as the *homeobox*.

Non-exonic ultra-conserved elements are often found in "gene deserts" that extend for more than a megabase. Of the non-exonic elements, there are 140 that are more than 10Kb away from any known gene, and 88 that are more than 100Kb away.

The set of 156 annotated genes that flank intergenic ultra-conserved elements is significantly enriched for developmental genes, and in particular, genes involved in early development, suggesting that many of the associated ultra-conserved elements may be enhancers of these early developmental genes.

Non-exonic elements that lie in introns are also often associated with developmental genes.

Many elements in the ultra-conservative set of 481 are considerably longer than 200bp. The longest elements (779bp, 770bp and 731 bp) all lie in the last three introns in the 3' portion of the DNA polymerase alpha catalytic subunit on chromosome X, along with other shorter ultra-conserved elements.

If the criterion "highly conserved" sequences with 99% identity (instead of 100% identity) is used, then there are 1 974 elements, of lengths up to 1 087bp in the human genome.

There are also 5 000 sequences of more than 100bp in length that are 100% identical in the human, rat and mouse

genomes. These appear to be essential for development in mammals and other vertebrates.

Tens of thousands more ultra-conserved sequences are present at lower percent identities. Thus, as much as 5% of the genome is more conserved than expected from neutral mutations occurring at random.

Ultra-conserved elements are indispensable

Researchers from the University of California, Santa Cruz in the United States and University of Queensland, Brisbane, Australia, suggest that these sequences are under negative "purifying" selection for more than 300 million years, and some for at least 400 million years; or else they have very low mutation rates, or they are subject to perfect repair. It means they must be 'vital' for survival.

The rate at which these sequences change in evolution is 20-fold less than the rest of the genome, including the protein coding regions.

The ultra-conserved elements show almost no natural variation in the human population. Only 6 out of 106 767 bp examined belong to validated SNPs (single nucleotide polymorphisms), whereas 119 are expected.

Surprise, surprise

But researchers revealed that mice with big chunks of such ultra-conserved sequences deleted get on very well without them.

Edward Rubin's team at the Lawrence Berkeley National Laboratory in California deleted two huge regions of DNA from mice. These regions contained nearly 1 000 highly conserved sequences shared between human and mouse. One region was 1.6 million DNA bases long, the other over 800 000 bases long. The researchers expected the mice to show big problems as a result of the deletions.

But the mutant mice were no different from normal mice in every respect: growth, metabolic functions, lifespan and overall development. "We were quite amazed," said Rubin, who presented the findings at a meeting of the Cold Spring Harbor Laboratory in New York earlier this year.

"It may say as much about our inability to detect any phenotypes as it says about the function of this region," said David Haussler of the University of California, Santa Cruz, whose team described the "ultra-conserved regions" in mammals, "What's most mysterious is that we don't know any molecular mechanism that would demand conservation like this." 