The Year in Science and Medicine

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Finished for the second time

Finishing the euchromatic sequence of the human genome

A list of authors and their affiliations appears in the Supplementary Information online
Nature 2004;431:931–945

Introduction: The sequence of the human genome encodes the genetic instructions for human physiology, as well as rich information about human evolution. In 2001, the International Human Genome Sequencing Consortium reported a draft sequence of the euchromatic portion of the human genome. Since then, the international collaboration has worked to convert this draft into a genome sequence with high accuracy and nearly complete coverage.

Results: The current genome sequence contains 2.85 billion nucleotides interrupted by only 341 gaps. It covers ~99% of the euchromatic genome and is accurate to an error rate of ~1 event per 100,000 bases. Many of the remaining euchromatic gaps are associated with segmental duplications and will require focused work with new methods.

Conclusions: The near-complete sequence, the first for a vertebrate, greatly improves the precision of biological analyses of the human genome including studies of gene number, birth and death. Notably, the human genome seems to encode only 20,000–25,000 protein-coding genes. The genome sequence reported here should serve as a firm foundation for biomedical research in the decades ahead.

Three years ago, a first draft of the human genome sequence had been completed with some gaps and errors remaining. These are now largely fixed. The 'finished' sequence has just 341 gaps remaining. Biologists now can go to the web to look up gene sequences in public online databases. The authors estimate that it covers 99% of the euchromatic portion of the genome and that the overall error rate is less than 1 error per 100,000 base pairs. This exceeds the original goals for the project. In one analysis the authors find 1,183 human genes that show evidence of having been recently 'born' by a process of gene duplication and divergence. They also find 37 genes that seem to have recently 'died' by acquiring a mutation that rendered the gene non-functional. The resulting pseudogene then slowly degrades and disappears. In another analysis, the authors mapped out segmental duplications, these make 5% of the genome that have duplicated in recent evolution. These include known genetic disorders involving segmental duplications, such as DiGeorge syndrome, but more are waiting to be discovered.

Yet, the human genome project is far from being finished. We still await the definitive catalogue of protein-coding genes. In the current paper, the number is estimated to be between 20,000 and 25,000, a humiliating figure as compared to the corn's 50,000 genes. Then, the task of sequencing the remaining 20% of the genome that lies within heterochromatin, the gene-poor, highly repetitive sequence that is implicated in the processes of chromosome replication and maintenance. Ahead, scientists will seek to understand how all the parts revealed by the genome sequence work together to make life.

The genome of the diatom, *Thalassiosira pseudonana*: ecology, evolution, and metabolism

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Science 2004;306:79–86

Introduction: Diatoms are unicellular algae with plastids acquired by secondary endosymbiosis. They are responsible for approximately 20% of global carbon fixation.

Results: This paper reports the 34 million-base pair draft nuclear genome of the marine diatom *Thalassiosira pseudonana* and its 129 thousand-base pair plastid and 44 thousand-base pair mitochondrial genomes. Sequence and optical restriction mapping revealed 24 diploid nuclear chromosomes. They identified novel genes for silicic acid transport and formation of silica-based cell walls, high-affinity iron uptake, biosynthetic enzymes for several types of polyunsaturated fatty acids, use of a range of nitrogenous compounds, and a complete urea cycle, all attributes that allow diatoms to prosper in aquatic environments.

We have seen genomic sequences of several species, so why is this one so important? We couldn't survive if it wasn't for diatoms. Better known as plankton, these are single-cell organisms found in both fresh water and the oceans. They are collectively responsible for 20% of the carbon fixed by photosynthesis throughout the globe – a contribution comparable to that of the world's rainforests. Their diverse watery lifestyle is helped by their wide genetic repertoire, which is now unraveled. But this paper is important for what is still unknown. Half of the genes discovered in the diatom have unknown functions, as a testament to how much is still ahead of us.

Mendel's rules reconsidered

Genome-wide non-mendelian inheritance of extra-genomic information in *Arabidopsis*

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Nature 2005;434:505–509

Introduction: Classical mendelian genetics is when allelic information is stably inherited from one generation to the next, resulting in predictable segregation patterns of differing alleles. This study shows that *Arabidopsis* plants homozygous for recessive mutant alleles of the organ fusion gene *HOTHEAD* (*HTH*) can inherit allele-specific DNA sequence information that was not present in the chromosomal genome of their parents but was present in previous generations.

Results: This previously undescribed process is shown to occur at all DNA sequence polymorphisms examined and therefore seems to be a general mechanism for extra-genomic inheritance of DNA sequence information.

Conclusions: These genetic restoration events are the result of a template-directed process that makes use of an ancestral RNA-sequence cache.

This is an extraordinary discovery suggesting that mendelian rules of inheritance are not as simple as was previously thought. The accidental findings have shown that plants may bypass the harmful

mutant genes inherited from their parents by reverting to the genetic code of their grandparents. Whereas *Arabidopsis* parents had two mutant copies of the *HOTHEAD* gene, which leads to a unique fused flower, 10% of the offspring had normal flowers. These progeny had rewritten one or both copies of the mutant gene, thereby reverting to the ancestral sequence of their (normal) grandparents. The paper suggests that the plants keep a cryptic copy of everything that was in the previous generation, even though it doesn't show up in the DNA. The most likely candidate is RNA, inherited from previous generations and used somehow as a 'backup' for correcting genes. Other faulty genes were also found to revert to their ancestral form, indicating that templates for many, if not all, genes are inherited. It wouldn't be surprising if the new DNA editing mechanism is present in people too.

Female diversity: 'la donna e mobile'

X-inactivation profile reveals extensive variability in X-linked gene expression in females

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Background: In female mammals, most genes on one X chromosome are silenced as a result of X-chromosome inactivation. However, some genes escape X-inactivation and are expressed from both the active and inactive X chromosome. Such genes are potential contributors to sexually dimorphic traits, to phenotypic variability among females heterozygous for X-linked conditions, and to clinical abnormalities in patients with abnormal X chromosomes.

Results: A comprehensive X-inactivation profile of the human X chromosome is presented, representing an estimated 95% of assayable genes in fibroblast-based test systems. In total, about 15% of X-linked genes escape inactivation to some degree, and the proportion of genes escaping inactivation differs dramatically between different regions of the X chromosome, reflecting the evolutionary history of the sex chromosomes. An additional 10% of X-linked genes show variable patterns of inactivation and are expressed to different extents from some inactive X chromosomes.

Conclusion: The analysis suggests a remarkable and previously unsuspected degree of expression heterogeneity among females.

The female genome differs from the male genome in several ways. The mammalian X and Y chromosomes arose from one pair of autosomes 300 million years ago; then the Y began to diverge through gene mutations. The Y chromosome endows the male with at least several dozen genes that are absent in the female. Here, the authors have used heterozygous fibroblast lines and assayed relative expression levels of polymorphic alleles. Ninety-four genes from 40 human samples were analyzed. In addition, gene expression was assessed in rodent/human somatic cell hybrids. The important conclusion of this analysis is that females will be even more variable with respect to X-linked gene expression than previously recognized. The incomplete nature of X-inactivation means that at least 15% of X-linked genes are expressed at characteristically higher (but often variable) levels in females than in males. Moreover, a minimum of an additional 10% of genes show heterogeneous X-inactivation, and thus differ in expression levels among females, whereas all males express a single copy of such genes. Because of this heterogeneity and the $\approx 15\%$ of genes that escape inactivation, the female genome differs from the male genome in at least four ways. First, the Y chromosome endows the male with at least several dozen genes that are absent in the female. Second, the incomplete nature of X-inactivation means that at least 15% of X-linked genes are expressed at variable levels in females and in males. Third, a minimum of an additional 10% of genes show heterogeneous X-inactivation and thus differ in expression levels among females, whereas all males express a single copy of such genes. And fourth, the random nature of X-inactivation indicates that females are mosaics of two cell populations with respect to X-linked gene expression. The large number of genes that escape inactivation,

and their non-random distribution on the chromosome, has implications for counseling individuals with X chromosome abnormalities, estimated at 1 in 650 live births. Thus, aneuploidy for Xp is more severe than aneuploidy for Xq. A word of caution: the current profile has been obtained in fibroblast cells and may or may not reflect the situation in other tissues relevant to specific disease phenotypes. In conclusion, the additional level of complexity demonstrated here will certainly offer new avenues to explore so far unexplained phenotypic variability in conditions such as Turner and Klinefelter syndromes.

Silent when you are diseased

Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs

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Introduction: RNA interference (RNAi) holds considerable promise as a therapeutic approach to silence disease-causing genes, particularly those that encode so-called ‘non-druggable’ targets that are not amenable to conventional therapeutics, such as small molecules, proteins, or monoclonal antibodies. The main obstacle to achieving in vivo gene silencing by RNAi technologies is delivery.

Results: This paper shows that chemically modified short interfering RNAs (siRNAs) can silence an endogenous gene encoding apolipoprotein B (apoB) after intravenous injection in mice. Administration of chemically modified siRNAs resulted in silencing of the apoB mRNA in liver and jejunum, decreased plasma levels of apoB protein, and reduced total cholesterol. It also shows that these siRNAs can silence human apoB in a transgenic mouse model. The mechanism of action for the siRNAs was proven to occur through RNAi-mediated mRNA degradation, and was determined that cleavage of the apoB mRNA occurred specifically at the predicted site.

Conclusions: These findings demonstrate the therapeutic potential of siRNAs for the treatment of disease.

Short interfering RNAs (siRNAs) are duplexes of RNA segments, where one of the strands is incorporated into a complex of proteins. This small RNA fragment guides the molecule to a complementary sequence on mRNA, then it either causes the mRNA to be cleaved by the protein complex or prevents it from being translated into a protein. It is intended to shut down disease-related genes in humans. We now learn that it works in mice. Chemically modified siRNAs have been able to silence the apoB mRNA in liver and jejunum, to decrease plasma levels of apoB protein, and to reduce total cholesterol. The idea of antisense-mediated inhibition of gene expression has been with us for about 30 years. Early work in the field used short, chemically synthesized strands of DNA that could be designed to selectively bind, through complementary base pairing, to any target mRNA of interest, and direct its cleavage through ribonuclease H. The invention reported here is that the system requires a single cholesterol conjugate per RNA duplex. Without cholesterol, there was no tissue delivery of the chemically modified siRNAs. Theoretically, synthesized siRNAs could be delivered to human cells, triggering sequence-specific silencing of complementary mRNA. It remains to be seen whether the cholesterol-conjugate approach can be used to silence other mutant genes.

Nonsense-mediated decay approaches the clinic

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Nat Genet 2004;36:801–808

Introduction: Nonsense-mediated decay (NMD) eliminates mRNAs containing premature termination codons, and thus helps limit the synthesis of abnormal proteins. New results uncover a broader role of NMD as a pathway that also affects the expression of wild-type genes and alternative-splice products.

Review: This review discusses the impact of NMD on the manifestation of human genetic diseases. It explores how an understanding of NMD accounts for phenotypic differences in diseases caused by premature termination codons. Specifically, it considers how the protective function of NMD sometimes benefits heterozygous carriers and, in contrast, sometimes contribute to a clinical picture of protein deficiency by inhibiting expression of partially functional proteins. Potential 'NMD therapeutics' will need to strike a balance between the general physiological benefits of NMD and its detrimental effects in cases of specific genetic mutations.

Nonsense mutations result in decreased abundance of affected mRNA transcripts, rather than in production of truncated proteins. NMD must distinguish a normal stop codon from a premature one. For this discrimination, both splicing and translation are crucial in mammals. A translation termination codon is generally interpreted as normal if no intron follows. Thus, most normal stop codons are located in the last exon, whereas NMD-activating premature termination codons are usually located further upstream. In addition to its role in eliminating 'faulty' transcripts encoding of potentially dominant negative proteins, NMD also has a role in controlling expression of 'normal' genes and is implicated in several essential physiological processes. NMD is not always beneficial: in some instances, truncated proteins encoded by mRNAs are fully or partially functional but are not synthesized because of NMD. For such cases, treatment strategies to reduce the effects of NMD are under evaluation. In contrast to its role in preventing dominant disease, NMD can also eliminate mRNAs that would otherwise result in the production of partly or fully functional truncated proteins. In such instances, interventions to prevent degradation of transcripts containing premature termination codons may be therapeutically useful. With broadened insight into the mechanism of NMD, continued development of new strategies to treat premature termination codons-related disease is a realistic goal.

Fear no more

A mechanism for impaired fear recognition after amygdala damage

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Nature 2005;433:68–72

Background: Ten years ago, the authors reported that SM, a patient with rare bilateral amygdala damage, showed an intriguing impairment in her ability to recognize fear from facial expressions. Since then, the importance of the amygdala in processing information about facial emotions has been borne out by a number of lesion and functional imaging studies. Yet the mechanism by which amygdala damage compromises fear recognition has not been identified.

Results: Returning to patient SM, it is now shown that her impairment stems from an inability to make normal use of information from the eye region of faces when judging emotions, a defect traced to a lack of spontaneous fixations on the eyes during free viewing of faces. Although SM fails to look normally at the eye region in all facial expressions, her selective impairment in recognizing fear is explained by

the fact that the eyes are the most important feature for identifying this emotion. Notably, SM's recognition of fearful faces became entirely normal when she was instructed explicitly to look at the eyes.

Conclusion: This finding provides a mechanism to explain the amygdala's role in fear recognition, and points to new approaches for the possible rehabilitation of patients with defective emotion perception.

This paper in *Nature* is exemplary for several reasons. First it shows how much can be learned from the observation of a single clinical case. Second, it exemplifies how complex perception can be and has several implications in daily life and for our clinical practice. This 38-year-old woman has a brain lesion encompassing all nuclei of the amygdala bilaterally, adjacent entorhinal cortex, yet spares all other subcortical and cortical structures, leaving her with essentially normal basic perception, memory, language and reasoning insofar as these do not involve the processing of emotional material. However, her processing of emotionally and socially meaningful information is impaired, as it is in non-human animals with amygdala damage. Here it is demonstrated that her specific defect in fear recognition is due to an inability to look at one in the eyes and interpret expressions.

The implications of this intriguing observation need to be explored. What is the amygdala's normal role in exploring social situations and looking at other people, and are these mechanisms altered in diseases such as phobias or autism that are thought to involve the amygdala? For us, pediatric endocrinologists, we know that women with Turner syndrome have impaired fear recognition and altered amygdala development [1]. These findings probably call for developing coping strategies for this specific deficit. We are just beginning to realize how the brain processes emotionally relevant cues in the environment, and the unusual features of SM will provide much food for future thought.

Date your mate

Unusually dynamic sex roles in a fish

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Introduction: Sex roles are typically thought of as being fixed for a given species. In most animals, males compete for females, whereas the females are more reluctant to mate. Therefore, sexual selection usually acts most strongly on males. This is explained by males having a higher potential reproductive rate than females, leading to more males being sexually active (a male-biased operational sex ratio). However, what determines sex roles and the strength of sexual selection is a controversial and much debated question.

Results: This large-scale field study shows a striking temporal plasticity in the mating competition of the two-spotted goby fish. Over the short breeding season, fierce male-male competition and intensive courtship behavior in males were replaced by female-female competition and actively courting females. Hence, sex role reversal occurred rapidly.

Conclusions: This is the first time that a shift in sex roles has been shown in a vertebrate. The shift might be explained by a large decline in male abundance, strongly skewing the sex ratio towards females. Notably, the sex role reversal did not occur at an equal operational sex ratio, contrary to established sex role theory.

Animal sex roles are termed 'conventional' when males compete for mates and 'reversed' when female competition occurs. Parental care and choosiness in mate choice are not included in this definition of sex roles. Hence, the term 'sex roles' as used here has a more specific meaning than it is in everyday language. Mating competition can be expressed through agonistic behavior that prevents conspecifics from mating, or through courtship to attract the opposite sex. The intensity of mating competition is largely explained by mate availability, expressed by the ratio of ready-to-mate males to ready-to-mate females. In most animals, males compete for females, whereas the females are more reluctant to mate. Therefore, sexual selection usually acts most strongly on males. Males adorn

themselves in most species more than females (but not so in humans). We now learn that there is flexibility in some vertebrate sex roles, which apparently can shift within the same population, and dynamic sex roles may be more widespread than currently known. This would have important implications for sexual selection processes. In particular, females might be subject to sexual selection more often than previously realized.

A new growth factor: restraint angiogenesis

Vasohibin as an endothelium-derived negative feedback regulator of angiogenesis

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J Clin Invest 2004;114:898–907

Introduction: Negative feedback is a crucial physiological regulatory mechanism, but no such regulator of angiogenesis has been established.

Methods and results: This study performed cDNA microarray analysis to survey VEGF-inducible genes in human endothelial cells (ECs). They report a novel angiogenesis inhibitor that is induced in ECs by angiogenic factors and inhibits angiogenesis in an autocrine manner. They characterized one such gene, *KIAA1036*, whose function had been uncharacterized. The recombinant protein inhibited migration, proliferation, and network formation by ECs as well as angiogenesis in vivo. This inhibitory effect was selective to ECs, as the protein did not affect the migration of smooth muscle cells or fibroblasts. Specific elimination of the expression of *KIAA1036* in ECs restored their responsiveness to a higher concentration of VEGF. The expression of *KIAA1036* was selective to ECs, and hypoxia or TNF- α abrogated its inducible expression.

Conclusions: As this molecule is preferentially expressed in ECs, it was designated ‘vasohibin’. Vasohibin is also an endothelium-derived negative feedback regulator of angiogenesis.

Angiogenesis is regulated in large part by the balance of various proangiogenic stimulators, such as VEGF, and a diverse group of endogenous inhibitors of angiogenesis, most of which are extrinsic to endothelial cells. With respect to the latter, until recently, none have appeared to be induced as a consequence of a specific, self-regulating, feedback inhibition response. The new inhibitor, called vasohibin, is selectively induced in endothelial cells by proangiogenic stimulatory growth factors such as VEGF; it appears to operate as an intrinsic and highly specific feedback inhibitor of activated endothelial cells engaged in the process of angiogenesis. We will probably hear soon enough how this factor responds or induces microvascular complications of diabetes.

Mechanism of the year: autophagy

The role of autophagy during the early neonatal starvation period

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Background: At birth the transplacental nutrient supply is suddenly interrupted, and neonates face severe starvation until supply can be restored through milk nutrients. Autophagy is the primary means for the degradation of cytoplasmic constituents within lysosomes.

Results: Neonates adapt to this adverse circumstance by inducing autophagy. The level of autophagy in mice remains low during embryogenesis; however, autophagy is immediately upregulated in various

tissues after birth and is maintained at high levels for 3–12 h before returning to basal levels within 1–2 days. Mice deficient for Atg5, which is essential for autophagosome formation, appear almost normal at birth but die within 1 day of delivery. The survival time of starved Atg5-deficient neonates (approx. 12 h) is much shorter than that of wild-type mice (approx. 21 h) but can be prolonged by forced milk feeding. Atg5-deficient neonates exhibit reduced amino acid concentrations in plasma and tissues, and display signs of energy depletion.

Conclusion: These results suggest that the production of amino acids by autophagic degradation of 'self' proteins, which allows for the maintenance of energy homeostasis, is important for survival during neonatal starvation.

Autophagy defends cells against invading group A *Streptococcus*

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Science 2004;306:1037–1040

Background: Autophagy mediates the bulk degradation of cytoplasmic components in eukaryotic cells in which a portion of the cytoplasm is sequestered in an autophagosome and eventually degraded upon fusion with lysosomes.

Results: The autophagic machinery could effectively eliminate pathogenic group A *Streptococcus* (GAS) within non-phagocytic cells. After escaping from endosomes into the cytoplasm, GAS became enveloped by autophagosome-like compartments and were killed upon fusion of these compartments with lysosomes. In autophagy-deficient Atg5^{-/-} cells, GAS survived, multiplied, and were released from the cells.

Conclusion: The autophagic machinery can act as an innate defense system against invading pathogens.

Endogenous MHC class II processing of a viral nuclear antigen after autophagy

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Science 2005;307:593–596

Background: CD4⁺ T cells classically recognize antigens that are endocytosed and processed in lysosomes for presentation on major histocompatibility complex (MHC) class II molecules.

Results: Endogenous Epstein-Barr virus nuclear antigen 1 (EBNA1) was found to gain access to this pathway by autophagy. On inhibition of lysosomal acidification, EBNA1, the dominant CD4⁺ T-cell antigen of latent Epstein-Barr virus infection, slowly accumulated in cytosolic autophagosomes. In addition, inhibition of autophagy decreased recognition by EBNA1-specific CD4⁺ T-cell clones.

Conclusion: Lysosomal processing after autophagy may contribute to MHC class II-restricted surveillance of long-lived endogenous antigens including nuclear proteins relevant to disease.

Earlier this year, Ciechanover and Herskho from Haifa and Rose from Irvine, Calif., USA, won the Nobel Prize in chemistry for the discovery of ubiquitin-mediated protein degradation. We now learn that autophagy, the process by which cells recycle cytoplasm and dispose of excess or defective organelles, has entered the research spotlight leading to the discovery of protein components driving this process. Cellular homeostasis requires a constant balance between biosynthetic and catabolic processes. Eukaryotic cells primarily use two distinct mechanisms for large-scale degradation, the proteasome and autophagy; but only autophagy has the capacity to degrade entire organelles. The three types of autophagy are macroautophagy, microautophagy, and chaperone-mediated autophagy.

This impressive series of papers puts autophagy at the center of body survival, innate and acquired immunity. The paper by Kuma et al. is of major interest for pediatricians particularly those involved in nutrition and metabolism in the neonatal period. It beautifully shows that autophagy is strongly

activated, in particular in the heart, soon after birth and that this process is essential to survival since mice deficient for the autophagy processes die soon after birth. This means that during fetal life, stocks are made at the cellular level, to be used right after birth, even before the general metabolism is activated and can provide blood-borne nutrients to fuel the cells in the essential organs of the body. These observations suggest that neonatal conditions might be due to defects in this pathway and that means to enhance it might improve outcome in stressed neonates. The other two papers further expand the spectrum of the function of autophagy: get rid of pathogens that have reached the cell cytoplasm and target viral proteins to the major histocompatibility complex for epitope display and elimination of the virally infected cell. Other observations published this year also suggest that viruses might have subverted the autophagy machinery for their own use [2]. Shintani and Klionsky [3] have also provided an extensive review on 'Autophagy in health and disease' analyzing the yin and yang of autophagy in various systems.

When a killer is executed

Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial

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Lancet 2004;364:1411–1420

Introduction: Development of an effective malaria vaccine could greatly contribute to disease control.

Methods: RTS,S/AS02A is a pre-erythrocytic vaccine candidate based on *Plasmodium falciparum* circumsporozoite surface antigen. This study assessed vaccine efficacy, immunogenicity, and safety in young African children. This was a double-blind, phase IIb, randomised controlled trial in Mozambique in 2,022 children aged 1–4 years. The study included two cohorts of children living in two separate areas, which underwent different follow-up schemes. Participants were randomly allocated three doses of either RTS,S/AS02A candidate malaria vaccine or control vaccines. The primary endpoint, determined in cohort 1 ($n = 1,605$), was time to first clinical episode of *P. falciparum* malaria (axillary temperature $\geq 37.5^{\circ}\text{C}$ and *P. falciparum* asexual parasitemia $>2,500/\mu\text{l}$) over a 6-month surveillance period. Efficacy for prevention of new infections was determined in cohort 2 ($n = 417$).

Results: Vaccine efficacy for the first clinical episodes was 29.9% ($p = 0.004$). At the end of the 6-month observation period, prevalence of *P. falciparum* infection was 37% lower in the RTS,S/AS02A group compared with the control group. Vaccine efficacy for severe malaria was 57.7%. In cohort 2, vaccine efficacy for extending time to first infection was 45.0% ($p < 0.0001$). The RTS,S/AS02A vaccine was safe, well tolerated, and immunogenic.

Conclusions: Development of an effective vaccine against malaria is feasible.

Malaria kills between 1 and 3 million people per year. A vaccine against this disease has shown promising results in a clinical trial in Mozambique. The hepatitis B protein is also included because it is effective at prompting an immune response. Although it did not prevent all children from being infected with the parasite, it kept them from becoming sick. The vaccine is considerably more effective at preventing the most dangerous form of the disease, lowering a recipient's risk of severe malaria by 58%. Among children between ages 1 and 2, the results looked even better: where it will not eradicate malaria, reducing the chance of severe malaria by 77% is a breakthrough.

A gain-of-function mutation of JAK2 in myeloproliferative disorders

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Background: Polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis are clonal myeloproliferative disorders arising from a multipotent progenitor. The loss of heterozygosity (LOH) on the short arm of chromosome 9 (9pLOH) in myeloproliferative disorders suggests that 9p harbors a mutation that contributes to the cause of clonal expansion of hematopoietic cells in these diseases.

Methods: Microsatellite mapping of the 9pLOH region and DNA sequencing was performed in 244 patients with myeloproliferative disorders (128 with polycythemia vera, 93 with essential thrombocythemia, and 23 with idiopathic myelofibrosis).

Results: Microsatellite mapping identified a 9pLOH region that included the Janus kinase 2 (JAK2) gene. In patients with 9pLOH, JAK2 had a homozygous G→T transversion, causing phenylalanine to be substituted for valine at position 617 of JAK2 (V617F). All 51 patients with 9pLOH had the V617F mutation. Of 193 patients without 9pLOH, 66 were heterozygous for V617F and 127 did not have the mutation. V617F is a somatic mutation present in hematopoietic cells. Mitotic recombination probably causes both 9pLOH and the transition from heterozygosity to homozygosity for V617F. Genetic evidence and in vitro functional studies indicate that V617F gives hematopoietic precursors proliferative and survival advantages. Patients with the V617F mutation had a significantly longer duration of disease and a higher rate of complications (fibrosis, hemorrhage, and thrombosis) and treatment with cytoreductive therapy than patients with wild-type JAK2.

Conclusions: A high proportion of patients with myeloproliferative disorders carry a dominant gain-of-function mutation of JAK2.

A unique clonal JAK2 mutation leading to constitutive signaling causes polycythemia vera

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Nature 2005;434:1144–1148

Background: Myeloproliferative disorders are clonal hematopoietic stem cell malignancies characterized by independency or hypersensitivity of hematopoietic progenitors to numerous cytokines. The molecular basis of most myeloproliferative disorders is unknown. On the basis of the model of chronic myeloid leukemia, it is expected that a constitutive tyrosine kinase activity could be at the origin of these diseases. Polycythemia vera is an acquired myeloproliferative disorder, characterized by the presence of polycythemia diversely associated with thrombocytosis, leukocytosis and splenomegaly. Polycythemia vera progenitors are hypersensitive to erythropoietin and other cytokines.

Results: The authors describe a clonal and recurrent mutation in the JH2 pseudo-kinase domain of the Janus kinase 2 (JAK2) gene in most (>80%) polycythemia vera patients. The mutation, a valine-to-phenylalanine substitution at amino acid position 617, leads to constitutive tyrosine phosphorylation activity that promotes cytokine hypersensitivity and induces erythrocytosis in a mouse model.

Conclusion: This unique mutation will permit a new molecular classification of these disorders and novel therapeutical approaches.

Four papers were published almost simultaneously that identified a new point mutation in the JH2 domain of the Janus kinase JAK2. In addition to the two papers cited above, reports by Baxter et al. [4] and Levine et al. [5] reported similar findings. The four mammalian Janus (JAK) kinases are recruited by ligand binding to cytokine receptors, where they are activated by trans-phosphorylation and, in turn, phosphorylate critical tyrosine residues on the receptor that can then serve as docking sites for members of the STAT (signal transducer and activation of transcription) family and for other

signaling molecules. Specific cytokine receptors recruit and activate distinct pairs of JAK and STAT proteins. JAK2 is the primary tyrosine kinase activated by erythropoietin. Many of the effects of JAK2 are mediated through the recruitment of STAT5 to phosphotyrosyl residues on the erythropoietin, interleukin-3, and granulocyte-macrophage colony-stimulating factor receptors. Together, these reports firmly establish somatic JAK2 mutations as a prevalent genetic lesion in polycythemia vera that plays an integral role in the disease phenotype. Based on the predicted JAK2 structure, the V-to-P substitution at codon 617 disrupts an autoinhibitory interaction between the JH2 and kinase domains of the protein. This results in activation of downstream pathways, including STAT5, Akt, and ERK. This mechanism is reminiscent of somatic PTPN11 mutations that constitutively activate the SHP-2 phosphatase in juvenile myelomonocytic leukemia. Germline-activating mutations of PTPN11 are involved in Noonan syndrome. These reports point to mutations of proteins involved in intracellular signaling networks as mechanisms of myeloproliferative disorders. We should also remember that the same signaling networks are involved in the transduction of hormonal signals and that STAT5b is a key element of growth hormone signaling.

Menu for life

The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%

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BMJ 2004;329:1447–1450

Introduction: Although the Polypill concept is promising in terms of benefits for cardiovascular risk management, the potential costs and adverse effects are its main pitfalls. The objective of this study was to identify a tastier and safer alternative to the Polypill – the Polymeal.

Methods: Data on the ingredients of the Polymeal were taken from the literature. The evidence-based recipe included wine, fish, dark chocolate, fruits, vegetables, garlic, and almonds. Data from the Framingham Heart Study and the Framingham Offspring Study were used to build life tables to model the benefits of the Polymeal in the general population from age 50, assuming multiplicative correlations.

Results: Combining the ingredients of the Polymeal would reduce cardiovascular disease events by 76%. For men taking the Polymeal daily represented an increase in total life expectancy of 6.6 years, an increase in life expectancy free from cardiovascular disease of 9.0 years, and a decrease in life expectancy with cardiovascular disease of 2.4 years. The corresponding differences for women were 4.8, 8.1, and 3.3 years.

Conclusion: The Polymeal promises to be an effective, non-pharmacological, safe, cheap, and tasty alternative to reduce cardiovascular morbidity and increase life expectancy in the general population.

While those of us over 50 are encouraged to take aspirin, vitamins, cholesterol-lowering pills and more, this study shows that tastier and safer alternatives seem to be as effective. Chocolate (100 g dark chocolate a day), 150 ml (only!) of wine, fish, nuts (68 g/day of almonds), garlic (2.7 g/day, that sounds like a lot to my wife), and fruit and vegetables will reduce the risk of cardiovascular disease by more than 75%. It is as good, and may be superior to taking heart-saving pills. Should you choose to accept it, you can devise your own menu using these ingredients, along with others if needed.

Evidence-based diagnostics

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BMJ 2005;330:724–726

Background: No international consensus exists on the methods for assessing diagnostic tests. Previous recommendations stress that studies of diagnostic tests should match the type of diagnostic question. Once the specificity and sensitivity of a test have been established, the final question is whether tested patients fare better than similar untested patients. This usually requires a randomised trial. Few tests are currently evaluated in this way.

Results: The authors propose an architecture for research into diagnostic tests that parallels the established phases in drug research. They have divided studies of diagnostic tests into four phases and use research on brain natriuretic peptide for diagnosing heart failure as an illustrative example. However, the architecture is applicable to a wide range of tests.

Conclusion: The four temporal phases of research provide a logical, stepwise procedure for development of diagnostic tests. However, the four phases do not apply to all diagnostic tests or provide an adequate basis for all types of diagnostic studies.

With increasingly sophisticated diagnostic tests available in all specialties of medicine, there appears to be a need for rationalization of their use, keeping the patient's health in mind. We all know that overuse of diagnostic tests called here 'defensive use' can create more trouble than good. This paper is a first step in hierarchizing steps in the development of tests. Like for clinical development of drugs, these steps go from phase I – determining the normal range of values through observational studies in healthy people to phase IV – determining the effects of introducing a new test into clinical practice by surveillance in large cohort studies. Pediatric endocrinology will be an important field for the evaluation of diagnostic tests through such a methodological filter, given the large number of new hormonal, genetic or radiological tests available.

Resist change

Easy ways to resist change in medicine

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BMJ 2004;329:1473–1474

Background: Numerous forces have been imposed on physicians to make them change their practice behaviors. Under the guise of 'quality improvement', managed care organizations, accrediting bodies, and the government are meddling in medicine. Even continuing medical education, previously a form of intellectual entertainment or a forum for much needed sleep, has refocused its efforts towards improving the care of patients.

Results: The authors describe available techniques that will allow doctors to practice unimpeded by new information that should induce change.

Conclusion: The authors conclude that using these time honored techniques will allow one to practice with the assurance that little thinking will be required that might distract you from the matter in hand – taking care of patients as you see fit – and will keep one in total control without any nagging feelings that there might be a better way to practice.

This paper, out of the humorous Christmas issue of the *BMJ*, contrasts with the previous one and puts back some common sense in modern medicine, and increasingly complex exercise, between technical

complexity, patients' needs, economical and administrative burden and legal implications. Putting the paper on evidence-based diagnosis and this paper on easy ways to resist changes in medicine back to back, offers no way out than a Confucian path to clinical medicine.

Food for thought: bigger isn't better

Cope's rule, hypercarnivory, and extinction in North American canids

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Science 2004;306:101–104

Introduction: Over the past 50 million years, successive clades of large carnivorous mammals diversified and then declined to extinction. In most instances, the cause of the decline remains a puzzle.

Results: This paper argues that energetic constraints and pervasive selection for larger size in carnivores lead to dietary specialization (hypercarnivory) and increased vulnerability to extinction. In two major clades of extinct North American canids, the evolution of large size was associated with a dietary shift to hypercarnivory and a decline in species durations.

Conclusions: Selection for attributes that promoted individual success resulted in progressive evolutionary failure of their clades.

The popular belief in the superiority of tall stature is based primarily on social bias rather than on a scientific foundation. But selection for individual traits and characteristics, though beneficial in the short run, can be detrimental in the long run. This paper shows that this likely happened to canids (the group that includes dogs) repeatedly during the past 50 million years, and perhaps to many large predators and mammals. Canid clades repeatedly show an increase in body size. Those clades that had the largest increase in body size and became specialized for attacking large prey, on the basis of teeth size and morphology, typically span only about 6 million years before becoming extinct, which is considerably less than for clades with smaller individuals and a more diverse diet. Studies indicating that taller people are more successful or more productive than shorter ones have ignored a wide range of evidence that shorter people are highly creative, long-lived and better for the environment. In the long run, they may outlive the big guys.

Small is efficient

A new small-bodied hominin from the Late Pleistocene of Flores, Indonesia

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Nature 2004;431:1055–1061

Introduction: Currently, it is widely accepted that only one hominin genus, *Homo*, was present in Pleistocene Asia, represented by two species, *Homo erectus* and *Homo sapiens*. Both species are characterized by greater brain size, increased body height and smaller teeth relative to Pliocene *Australopithecus* in Africa.

Results: This paper reports the discovery, from the Late Pleistocene of Flores, Indonesia, of an adult hominin with stature of 1 m and endocranial volume of 380 cm³. The combination of primitive and derived features assigns this hominin to a new species, *Homo floresiensis*.

Conclusions: The most likely explanation for its existence on Flores is long-term isolation, with subsequent endemic dwarfing, of an ancestral *H. erectus* population. Importantly, *H. floresiensis* shows that

the genus *Homo* is morphologically more varied and flexible in its adaptive responses than previously thought.

For a pediatric endocrinologist the revelation of the year is a population of small man-like hominids that survived until about 18,000 years ago on a remote Indonesian island. They were <1 m tall, and had a body weight of 20 kg and a brain size of 380 cm³ (smaller than that of a chimpanzee). It is interesting to speculate which selective pressures were active to select for dwarfism on this island. A favorite theory that was proposed is that these dwarfs would have evolved to occupy a niche of abundant food left vacant by the lack of small mammals on this island. Another theory is that small-bodied animals were less likely to starve than large-bodied animals in harsh conditions. It will be interesting to learn what mechanisms evolution used to select for size. Was it growth hormone? Its receptor? Bone morphogenetic proteins? The fact that these creatures relate to the *Homo erectus* rather than to us, *Homo sapiens*, may imply an unexpected mechanism.

Mass extinction

Ecosystem remodeling among vertebrates at the Permian-Triassic boundary in Russia

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Nature 2004;432:97–100

Introduction: The mass extinction at the Permian-Triassic boundary, 251 million years ago, is accepted as the most profound loss of life on record. Global data compilations indicate a loss of 50% of families or more, both in the sea and on land, and these figures scale to a loss of 80–96% of species, based on rarefaction analyses. This level of loss is confirmed by local and regional-scale studies of marine sections, but the terrestrial record has been harder to analyze in such close detail.

Methods and Results: Here the authors document the nature of the event in Russia in a comprehensive survey of 675 specimens of amphibians and reptiles from 289 localities, spanning 13 successive geological time zones in the South Urals basin. There was a profound loss of genera and families, and simplification of ecosystems, with the loss of small fish-eaters and insect-eaters, medium and large herbivores and large carnivores. Faunal dynamics also changed, from high rates of turnover through the Late Permian period to greater stability at low diversity through the Early Triassic period. Even after 15 million years of ecosystem rebuilding, some guilds were apparently still absent – small fish-eaters, small insect-eaters, large herbivores and top carnivores.

The most drastic annihilation of life that we know of happened 250 million years ago, and is recognized as the Permian-Triassic mass extinction, lasting for 500,000 years. Simplification of ecosystems, consumed mostly small fish-eaters and insect-eaters, medium and large herbivores and large carnivores. It was associated with a loss of 50% of families or more, both in the sea and on land, and these figures scale to a loss of 80–96% of all species. The damage was still apparent after 15 million years of ecosystem rebuilding. At a time when there is so much focus on global change and threats to biodiversity, it is surprising how little we know about this event. The cause was probably massive outpourings of basalt lava in Southern Ural, which triggered global warming and anoxia, and possibly a runaway greenhouse effect associated with repeated release of gas hydrates. The mechanisms for today's global warming may be different, but the lesson from Earth's distant history is important to learn.

Carbonyl sulfide-mediated prebiotic formation of peptides

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Science 2004;306:283–286

Introduction: Discussion of prebiotic chemistry assumes that amino acids and nucleotides were first formed on the Earth or brought to it in comets and meteorites, and then condensed non-enzymatically to form oligomeric products. However, attempts to demonstrate plausibly prebiotic polymerization reactions have met with limited success.

Results: This study shows that carbonyl sulfide (COS), a simple volcanic gas, brings about the formation of peptides from amino acids under mild conditions in aqueous solution.

Conclusions: Depending on the reaction conditions and additives used, exposure of amino acids to COS generates peptides in yields of up to 80% in minutes to hours at room temperature.

Prebiotic chemistry deals with the origins of the first simple life forms to live on earth, roughly 3.6 billion years ago. But how did amino acids or nucleotide monomers condense to form oligomers. This paper suggests that carbonyl sulfide (COS), a gas that is a product of volcanic eruptions, brings about the formation of peptides from amino acids under mild conditions in water solution. The reaction is catalyzed by iron or copper ions, also abundant in volcanic gasses, to increase its yields, in some cases dramatically. The authors suggest that COS may have functioned near its volcanic sources in polymerization of amino acids into peptides, then peptides long enough to be irreversibly adsorbed near the source of the COS were subject to slow chain elongation. These simple forms must have run away from volcano fast enough to survive.

ET on Mars?

Detection of methane in the atmosphere of Mars

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Science 2004;306:1758–1761

Introduction: This paper reports a detection of methane in the Martian atmosphere by the Planetary Fourier Spectrometer onboard the Mars Express spacecraft.

Results: The global average methane mixing ratio was found to be 10 ± 5 parts per billion by volume (ppbv). However, the mixing ratio varies between 0 and 30 ppbv over the planet.

Conclusions: The source of methane could be either biogenic or non-biogenic, including past or present subsurface microorganisms, hydrothermal activity, or cometary impacts.

See also Squyres et al. [6]

The likelihood that we will encounter life in distant space stars is minimal. Out of the about 10 billion billion stars in our universe, the closest one to us is 4.2 light-years away. It was therefore rewarding to learn this year that nearby, on our neighbor Mars, billions of years ago enough water pooled on the surface for long enough to allow the possibility of life. It seems that Mars of several billion years ago was warm enough and wet enough to have a shallow, salty sea. On Earth, methane is almost entirely derived from biological sources. The detection of methane is the clearest indicator so far of the possibility of life on Mars. Mars resembles Earth more than any other planet in our solar system, and studying its atmosphere gives us a greater understanding of our own. How the methane got to Mars is the big question, and there are several possible sources. The most exciting scenario is that

methanogens – microbes that consume the Martian hydrogen or carbon monoxide for energy and exhale methane – dwell in colonies out of sight beneath the surface of the planet. Another option is that a comet could have struck Mars, which would have left methane behind.

Like father like son

Modeling the recent common ancestry of all living humans

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Nature 2004;431:562–566

Introduction: If a common ancestor of all living humans is defined as an individual who is a genealogical ancestor of all present-day people, the most recent common ancestor (MRCA) for a randomly mating population would have lived in the very recent past. However, the random mating model ignores essential aspects of population substructure, such as the tendency of individuals to choose mates from the same social group, and the relative isolation of geographically separated groups.

Methods and Results: One model, designed for simplicity and theoretical insight, yields explicit mathematical results through a probabilistic analysis. A more elaborate second model, designed to capture historical population dynamics in a more realistic way, is analyzed computationally through Monte Carlo simulations. Recent common ancestors emerge from the two models, incorporating substantial population substructure.

Conclusions: These analyses suggest that the genealogies of all living humans overlap in remarkable ways in the recent past. In particular, the MRCA of all present-day humans lived just a few thousand years ago in these models. Moreover, among all individuals living more than just a few thousand years earlier than the MRCA, each present-day human has exactly the same set of genealogical ancestors.

How far back in time must we go to find an individual who was the ancestor of all present-day humans? The existence of such a ‘most recent common ancestor’ should not surprise: the growth in the population of our ancestors is close to exponential as we trace them back in time. This is true for anybody’s ancestors, yet, there is an overlap between the ancestors of two or more individuals. In simplified models, which assume random mating, the average number of generations back to a universal common ancestor has been estimated to be around $\log_2 n$, where n is the population size. For the present human population of size 6 billion, it would be 33 generations, corresponding to 800 years. This is surprisingly recent. And an even more surprising conclusion from such models is that, only a little farther back in time, a large fraction of the population will be the ancestors of everybody alive today. The remaining individuals back then will be the ancestors of no one. The simplicity of this model is clear. Key missing factors are geography (population structure) and history (population growth). The authors carried out simulations based on several scenarios, incorporating different degrees of population growth and different degrees of isolation of subpopulations, with occasional migration linking these subpopulations. In several sets of estimates, the mean time back to the universal ancestor is 2,300–5,000 years. Interestingly, the Jewish calendar counts now 5,765 years since the Creation. Combining pedigree and genetic ancestry will become important, both for data analysis and in exploring properties of population model. One wonders how much genetic material did the universal ancestor pass on to the present population? But what about that for a non-universal ancestor from the same time? [7]

Endurance running and the evolution of *Homo*

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Nature 2004;432:345–352

Background: Striding bipedalism is a key derived behavior of hominids that possibly originated soon after the divergence of the chimpanzee and human lineages. Although bipedal gaits include walking and running, running is generally considered to have played no major role in human evolution because humans, like apes, are poor sprinters compared to most quadrupeds.

Results: The authors assess how well humans perform at sustained long-distance running, and review the physiological and anatomical bases of endurance running capabilities in humans and other mammals. Judged by several criteria, humans perform remarkably well at endurance running, thanks to a diverse array of features, many of which leave traces in the skeleton.

Conclusion: The fossil evidence of these features suggests that endurance running is a derived capability of the genus *Homo*, originating about 2 million years ago, and may have been instrumental in the evolution of the human body form.

In the outskirts of every city in the industrialized world, one can see joggers running in circles and apparently uselessly burning energy every weekend. Being one of them, I (J.C.C.) always wondered what pushes me to this activity even in bad weather. Endorphins are often invoked as a mechanism for this apparent addiction. Here, Bramble and Lieberman review the physiology and metabolic performance across species and analyze primate's skeletal evolution. They end up with the somewhat surprising conclusion that *Homo* is the best-fitted mammalian genus when it comes to endurance running. Not surprisingly, we do poorly when it gets to sprinting. In contrast, our metabolic cost of transport decreases with speed at endurance running speeds, as opposed to horses for instance who have a U-shaped curve, meaning that increased speed means increased energy demand. Other features, in particular limb strength and size, make us more adapted to endurance running than primates.

Many hypotheses have been proposed for the role of walking (particularly long-distance trekking) in human evolution. Given human endurance running performance capabilities, as well as the many derived features that appear to make them possible, it is also necessary to ask whether, when and why long-distance running may have played a role in human evolution. Most of the major structural bases of endurance running that can be observed in the skeleton are present in early *Homo erectus*. The hypothesis that endurance running evolved in *Homo* for scavenging or even hunting therefore suggests that endurance running may have made possible a diet rich in fats and proteins thought to account for the unique human combination of large bodies, small guts, big brains and small teeth. Today, endurance running is primarily a form of exercise and recreation, but its roots may be as ancient as the origin of the human genus, and its demands a major contributing factor to the human body form.

Short-lived chlorine-36 in a Ca- and Al-rich inclusion from the Ningqiang carbonaceous chondrite

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Proc Natl Acad Sci USA 2005;102:1306–1311

Results: Excesses of sulfur-36 in sodalite, a chlorine-rich mineral, in a calcium- and aluminum-rich inclusion from the Ningqiang carbonaceous chondrite linearly correlate with chlorine/sulfur ratios, providing direct evidence for the presence of short-lived chlorine-36 (with a half-life of 0.3 million years) in the early solar system. Different from other short-lived radionuclides, chlorine-36 was introduced into the inclusion by solid-gas reaction during secondary alteration. The alteration reaction probably took place at least 1.5 million years after the first formation of the inclusion.

Conclusions: This discovery supports a supernova origin of short-lived nuclides, but presents a serious challenge for local irradiation. Furthermore, the short-lived Cl-36 may serve as a unique fine-scale chronometer for volatile-rock interaction in the early solar system because of its close association with aqueous and/or anhydrous alteration processes.

For years, astronomers have believed that the solar system formed from a slowly condensing cloud of dust and gas; but this traditional view is now being challenged. New meteorite data supports a controversial theory that the violent explosion of a star was involved in the creation of the sun and its planets. The primitive space rock contains signs that a short-lived, radioactive form of chlorine may have been present in the early solar system, and that the source of this isotope was a supernova or an exploding star. The new theory proposes that our star and its planetary system were born in a dense interstellar cloud, or nebula, filled with short-lived, massive stars that exploded with immense energy and an intense release of radiation. If the controversial theory is supported by future work, it may have implications for understanding properties such as the size and shape of the solar system, the physical make-up of earth and the chemistry that led to life.

Now here, now there

Deterministic quantum teleportation with atoms

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Nature 2004;429:734–737

Introduction: Teleportation of a quantum state encompasses the complete transfer of information from one particle to another. The principles of quantum mechanics dictate that any measurement on a system immediately alters its state, while yielding at most one bit of information. The transfer of a state from one system to another might therefore appear impossible. Teleportation using pairs of entangled photons has been demonstrated, but such techniques are probabilistic, requiring post-selection of measured photons.

Results: Deterministic quantum-state teleportation between a pair of trapped calcium ions was utilized. Following closely the original proposal, the authors create a highly entangled pair of ions and perform a complete Bell-state measurement involving one ion from this pair and a third source ion. State reconstruction conditioned on this measurement is then performed on the other half of the entangled pair. The measured fidelity is 75%, demonstrating unequivocally the quantum nature of the process.

See also Barrett et al. [8].

Ever since physics accepted Planck's quantum theory and the Heisenberg's uncertainty principle, we know that an atom cannot have both a specific location and a determined velocity at the same time, which set the stage for teleportation, and accomplishment was only a matter of setting the experiment right. The concept of teleportation is hard to grasp, but using the fax machine, we can already transfer the information in a book at almost the speed of light. The information can then be reprinted at the other side in an identical format. Modern technology decreased the time required for transfer of objects, but can it eliminate the time required altogether? Classical physics cannot exclude future scanning of more complex objects and transfer of the information. These two reports describe teleportation of an atom – the distant transfer of the atom's qualities, without making the way between them, and in no time. Atoms disappeared in one lab and appeared in another in no time. What are the chances to teleport more complex objects? Theoretically this would be possible, though it is going to be difficult.

Strong in force

The Nobel Prize in Physics 2004

<http://nobelprize.org/physics/laureates/2004/public.html>

The Standard Model of Nature counts four basic forces. The first is gravity. Among particles like electrons and protons, the force of gravity is extremely weak. The three other forces or interactions that are applicable to the microcosmos are the electromagnetic interaction, the weak interaction and the strong interaction. This is the only mathematical description, which takes into account both Einstein's theory of relativity and quantum mechanics.

The electromagnetic interaction is responsible for friction, magnetism and the fact that neither objects nor we fall through the floor. The electromagnetic interaction that binds an electron and a proton in a hydrogen atom is the inconceivably large number of 1,041 times stronger than gravity. The weak interaction is carried by the bosons, particles that, unlike the photon and the graviton, have very large masses (approximately 100 proton masses!). That is why the interaction has a short range. It acts on both quarks and leptons and is responsible for some radioactive decays.

The discovery, which was awarded this year's Nobel Prize, is of decisive importance for our understanding of the force that ties together the smallest pieces of matter – the quarks, the constituents that build protons, neutrons and the nuclei. David Gross, David Politzer and Frank Wilczek have through their theoretical contributions on the Strong Force made it possible to complete our understanding of the strong interaction – often called the *color interaction*. When analyzing an everyday phenomenon like a coin spinning on a table, its movements are in fact determined by the fundamental forces between the basic building blocks – protons, neutrons, electrons. In fact, about 80% of the coin's weight is due to movements and processes in the interior of the protons and neutrons – the interaction between quarks, the strong or color force. This year's Nobel Prize is about this interaction, the strong or color force.

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