tivity, especially the latter, have revealed that individuals both compete and cooperate by making inferences about what others know and intend (*10*, *11*). These studies have revolutionized our understanding of what chimpanzees think and feel, raising profound philosophical questions about the nature of thought without language, as well as ethical questions concerning the rights and welfare of these animals (*12*).

Constraining our continued understanding of this wonderful animal is one annoying hurdle: our own species. In the very near future, we may ironically face the possibility of having a detailed map of the chimpanzee genome, but no individuals to study. Illegal hunting, the bushmeat trade, and deforestation are destroying chimpanzee populations (see, for example, www.chimpcollaboratory.org). If the same amount of effort that is going into genetic analyses went into chimpanzee conservation and behavioral biology, not only would we save this species from extinction, but we would write the most detailed story of our past—as rich as the Bible, but grounded in science.

References and Notes

1. The Chimpanzee Sequencing and Analysis Consortium, *Nature* **437**, 69 (2005).
2. J. Goodall, *The Chimpanzees of Gombe: Patterns of Behavior* (Belknap/Harvard, Cambridge, MA, 1986).
3. M. A. Huffman, R. W. Wrangham, in *Chimpanzee Cultures.* R. W. Wrangham, W. C. McGrew, F. B. M. de Waal, P. G. Heltne, Eds. (Harvard Univ. Press, Cambridge, MA, 1994), pp. 129–148.
4. A. Whiten *et al.*, *Nature* **399**, 682 (1999).
5. T. Matsuzawa, *Primate Origins of Human Cognition and Behavior* (Springer-Verlag, Berlin, 2002).
6. M. L. Wilson, M. D. Hauser, R. W. Wrangham, *Anim. Behav.* **61**, 1203 (2001).
7. R. W. Wrangham, D. Peterson, *Demonic Males* (Houghton Mifflin, New York, 1996).
8. M. D. Hauser, *Wild Minds: What Animals Really Think* (Holt, New York, 2000).
9. F. B. M. de Waal, *Chimpanzee Politics: Power and Sex Among Apes* (Harper & Row, New York, 1982).
10. D. Premack, A. Premack, *Original Intelligence* (McGraw-Hill, New York, 2002).
11. M. Tomasello, J. Call, B. Hare, *Trends Cognit. Sci.* **7**, 153 (2003).
12. P. Cavalieri, P. Singer, *The Great Ape Project: Equality Beyond Humanity* (St. Martin's, New York, 1994).

13. I thank three of my closest colleagues for comments on this essay: F. de Waal, B. Hare, and R. Wrangham.

10.1126/science.1111421

GENOMICS

Thoughts on the Future of Great Ape Research

Edwin H. McConkey and Ajit Varki

When the Human Genome Project was established in 1991, the planners wisely included sequencing the genomes of model organisms in the project's goals. At that time, the only nonhuman mammalian genome scheduled for sequencing was that of the laboratory mouse. Although the relevance of the mouse genome for interpreting the human sequence was beyond dispute, some biologists were disappointed that no nonhuman primate genome had been included. The remarkable similarity of the chimpanzee genome to that of humans was already predicted from overall DNA comparisons, and it seemed clear that questions about the genetic basis for human uniqueness would eventually require detailed comparisons with the genomes of great apes (*1*), our closest evolutionary relatives. A formal presentation of the need for sequencing the chimpanzee genome was published in 1997 (*2*). Soon thereafter it was pointed out (*3*) that there should also be a project to increase our knowledge of the great ape "phenome" (the complete body of information about an organism's phenotype under various environmental conditions), about which very little is known. Scientists from a variety of disciplines rallied in support of sequencing the chimpanzee genome, also citing biomedical reasons and the potential importance for proper care and conservation of great apes (*4*, *5*).

We now have a draft sequence of the common chimpanzee genome (*Pan troglodytes*) and a detailed comparison with the human genome (*6*). The results include extensive information on comparative genomics, such as the number of single base pair and insertion/deletion differences and transposable elements unique to either human or chimpanzee. The report clarifies much previously conflicting or confusing information in existing human nucleotide sequence databanks and addresses several important questions about genomic and population evolution mechanisms. It also adopts a rational orthologous chromosomal numbering system to facilitate comparisons of human and ape genomic organization (*7*).

Can we now provide a DNA-based answer to the fascinating and fundamental question, "What makes us human?" Not at all! Comparison of the human and chimpanzee genomes has not yet offered any major insights into the genetic elements that underlie bipedal locomotion, a big brain, linguistic abilities, elaborated abstract thought, or any other unique aspect of the human phenome. This state of affairs may seem disappointing, but it is merely the latest example of a generalization that genomics research has already established—interpretation of DNA sequences requires functional information from the organism that cannot be deduced from sequence alone. Functional genomics investigations must determine where a gene is expressed within an organism, when it is expressed during development and life history, and what the level of expression is at various times. Furthermore, these data must be integrated with information about the related phenotypes, as well as critical environmental influences under which the genotype generates the phenotype (see the figure).

There are three general reasons for substantially increasing research on chimpanzees (and the other great apes—bonobos, gorillas, and orangutans): First, to understand the contribution of genomic DNA to human and great ape evolution; second, to improve our understanding of human and ape phenomes (at all levels, from molecular to behavioral to states of diseases); and third, to help preserve populations of these important human relatives. These goals must be pursued in the face of challenging ethical issues that still need to be resolved by open debate.

Understanding the genetic basis of uniquely human traits will require increasing the accuracy and completeness of the currently available chimpanzee genome sequence, as well as sequencing other primate genomes as out-groups. The genomes of the orangutan and the rhesus macaque are currently being sequenced, but other genomes are needed to obtain a complete picture. Among other benefits, such multispecies comparisons are essential for identifying human-specific coding and regulatory regions.

A parallel requirement is the comparison of human gene expression with those of chimpanzees and other primates. There are formidable obstacles to achieving this goal, the most obvious of which is obtaining experimental material from great apes. It is not ethically acceptable to sacrifice a great ape simply to obtain tissue samples.

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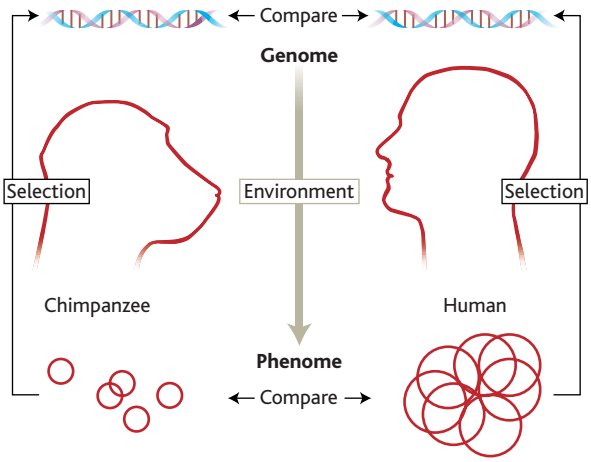
Studies of great apes should follow guidelines generally similar to those for research on human subjects. Thus, there is a need for new funding to support development of a network among current holders of captive great apes (including primate facilities, great ape sanctuaries, and zoos) to guarantee that tissue samples can be obtained quickly from each great ape that dies of natural causes, or has to be euthanized because of incurable suffering. Autopsy samples need to be preserved for histological analysis and used as source materials for studies of gene expression and cDNA libraries. Such samples can also be used for a wide variety of other "omic" comparisons (including proteomics, glycomics, and lipomics). Because every tissue is made up of multiple cell types, such approaches can still miss important differences in minor cell types. Thus, parallel histological comparisons must occur, using multiple probes to detect differences.

Examination of adult tissues, however, will still not allow us to understand gene expression and its consequences during development, which may well be the time when many of the crucial differences between humans and the great apes are expressed. This concept was suggested decades ago by King and Wilson (*8*), and studies since then have given us no reason to reject that hypothesis. Analysis of gene expression during prenatal development can be approached with three experimental strategies: transgenesis, stem cells, and direct study of developmental samples.

Transfer of human genes into mice has been fundamental to the analysis of human gene function. Comparative analysis of human and chimpanzee orthologous genes in transgenic mice is now certain to be pursued. Of course, there are limits to what one can deduce about the phenotypic effects of human or ape genes in mice. This is particularly true for the brain, skin, innate immune system, and reproductive system, wherein primates have undergone considerable functional divergence from rodents. However, ethical, fiscal, and practical considerations will make the idea of transgenic apes moot. Thus, we should expect that the need for transgenic monkeys will arise, and deciding on the ideal model for such experiments will not be easy. Given ethical and practical issues and the longer generation-time of monkeys, such studies will require much thought, patience, and long-term funding.

Embryonic stem cell cultures from humans are a subject of intense interest. Although creation of stem cell lines from ape embryos will be just as difficult technically, it represents a feasible experimental approach that causes no lasting harm to the animals from which gametes are obtained for in vitro fertilization. As technical progress is made with human stem cells, this knowledge can be applied to chimpanzee stem cells, providing a major source of information on gene expression in several embryonic and differentiated cell types, during various stages of in vitro development. If current approaches to tissue and organ engineering with human stem cells are successful, parallel studies of chimpanzee equivalents could provide further resources to study expression of genes and gene products and contribute to treatment of great ape diseases in the future.



What makes us human? This question may be answered by comparison of human and chimpanzee genomes and phenomes, and ultimately those of other primates. To this end, we need to understand how genotype generates phenotype, and how this process is influenced by the physical, biological, and cultural environment.

Material for direct analysis of gene expression during embryonic development can, in principle, be obtained by controlled breeding and surgical termination of pregnancies. This approach is already well established for monkeys such as the rhesus macaque. A thorough study of gene expression during monkey embryonic development would be expensive, but it should be undertaken (*9*), perhaps only after studies of transgenic mice and chimpanzee stem cells have defined critical experimental questions that cannot be otherwise answered. We do not envision this being done with great apes because of ethical and practical considerations. As with humans, however, great ape samples may become available in the course of birth control or medical care.

The second reason for expanding research on chimpanzees and other apes is the lack of information on their phenotypes (*3*). The utility of the human genome has been greatly aided by our vast knowledge of the human phenome in areas ranging from anatomy to cognitive function. In contrast, our knowledge of the great ape phenome is inadequate, except in a few arenas such as behavior and ecology. Worse, extant information on great apes is in many scattered sources spanning the last century, and some accepted "facts" actually represent folklore derived from misinterpretations or assumptions made in popular science literature. Thus, there is no easy way to reliably ascertain all the known and unknown differences between humans and great apes. One possibility (*10*) is to develop a Web-based "Museum of Comparative Anthropogeny" that would catalog information about human-specific differences from great apes that is scattered throughout the literature. Having a centralized resource of such information could lead to new conceptual insights and multidisciplinary interactions and also point to ethically acceptable studies that would help to explain human-ape differences. Regardless, interpreting the results of functional genomics studies will require more information about ape phenomes. Thus, there should be substantially increased funding for studies on great ape anatomy, physiology, biochemistry, neurobiology, cognitive functions, behavior, and ecology. All such research should be done following ethical principles like those currently used in human studies. Much can also be learned in the course of providing outstanding medical care, as has been the case for humans. Increased knowledge about ape phenomes will likely be helpful for understanding some human diseases (*5*).

The third reason for expanding research on chimpanzees and other great apes is that the more we know about these species, the better we can care for them. This will be particularly important for captive apes, but could also have an impact on maintaining healthy wild populations (for example, by vaccinating them against human diseases). In this regard, making practical use of all the functional and behavioral knowledge arising from such research will require a significant increase in financial support for the optimal maintenance of captive great apes, and to facilitate survival of currently endangered wild populations. One way to coordinate funding for ape research and care is to create a Great Ape Conservation Trust that would receive 10% of all grant funds awarded by government agencies for research on ape genomes, phenomes, or behavior. The Trust could be administered by an agency that does not award research grants; instead, it would

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award grants only for the support of captive animals and the conservation of wild populations. The agency that administers the Trust could be either a governmental or nongovernmental group that already exists, or a new organization with representatives from various interest groups, particularly those with firsthand knowledge about conservation issues. The Trust could also be authorized to solicit and receive funds from nongovernmental sources.

With the sequencing of the chimpanzee genome, we have now reached the end of the beginning, and can start down the long road toward fully understanding our relationships to these closest evolutionary cousins. If the road is taken with intellectual and ethical care, there is much to gain, for both them and us.

References and Notes

1. The term "great ape" is used here in the colloquial sense. In the commonly used classification, these species are now grouped with humans in the family Hominidae, and humans belong to the tribe Hominini, along with chimpanzees and bonobos.
2. E. H. McConkey, M. Goodman, *Trends Genet.* **13**, 350 (1997).
3. A. Varki *et al.*, *Science* **282**, 239 (1998).
4. E. H. McConkey, A. Varki, *Science* **289**, 1295 (2000).
5. A. Varki, *Genome Res.* **10**, 1065 (2000).
6. Chimpanzee Sequencing and Analysis Consortium, *Nature* **437**, 69 (2005).
7. E.H. McConkey, *Cytogenet. Genome Res.* **105**, 157 (2004).
8. M.C.King, A. C. Wilson, *Science* **188**, 107 (1975).
9. E. H. McConkey, *Trends Genet.* **18**, 446 (2002).
10. M. V. Olson, A. Varki, *Science* **305**, 191 (2004).

11. The opinions expressed are strictly those of the authors. We thank K. Krauter, J. Moore, P. Gagneux, and N. Varki for helpful comments. Supported by the G. Harold and Leila Y. Mathers Charitable Foundation.

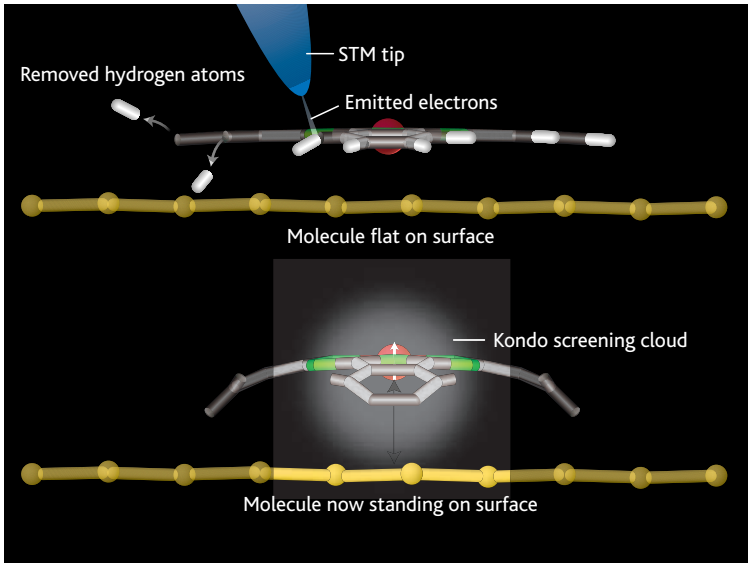
10.1126/science.1113863

PHYSICS

Manipulating Magnetism in a Single Molecule

Michael F. Crommie

The size of magnetic objects that can be manipulated in condensed-matter environments has decreased over the last 50 years, from bulk ferromagnets to thin films, nanocrystals, clusters, and now to single atoms and molecules (*1*–*7*). The single-atom or single-molecule regime is especially interesting because magnetism arises in this case from very few unpaired electronic spins and is thus quantum mechanical in nature. This property opens new opportunities that range from basic quantum impurity studies to quantum information and spintronics applications (*8*). Molecular systems, in particular, provide a useful means for "packaging" quantum spin centers, because molecules are structurally and electronically very flexible (*7*). This is readily seen in the work of Zhao *et al.* (*9*) on page 1542 of this issue. They show that it is possible to tune the spin behavior of a magnetic cobalt ion trapped within a single molecule by pruning the ligands of the molecule with the tip of a scanning tunneling microscope (STM).



Molecular magnetic surgery. (**Top**) An STM tip is used to snip hydrogen atoms from a single cobalt phthalocyanine molecule lying on a gold surface. (**Bottom**) The trimmed molecule protrudes from the surface and is surrounded by a cloud of electrons that represent the Kondo screening cloud about the cobalt ion spin.

Zhao *et al.* observed this behavior by tunneling electrons from the tip of an STM into a single cobalt phthalocyanine (CoPc) molecule sitting on a gold surface, thereby performing a type of local electron spectroscopy. For pristine CoPc molecules they observed the d-orbital of the inner cobalt ion to be an energetically broad resonance lying below the Fermi energy (E_F, the energy of the highest occupied electronic level). After plucking hydrogen atoms from the periphery of the molecule with their STM, however, the broad d-resonance was replaced by a much narrower resonance pinned at E_F, indicating a change in the magnetic nature of the molecule (see the figure).

Monitoring the d-orbital of a magnetic nanostructure in this way allows one to study its magnetic properties. This is because magnetism in transition-metal ions (like the cobalt ion in CoPc) arises from unpaired spins residing in d-orbitals. When a single cobalt atom or cobalt-carrying molecule contacts a metal surface, the d-orbital hybridizes with the continuum states of the surface and broadens energetically into a resonance. If the resonance shifts below E_F, then electrons are transferred to the d-level, whereas if the resonance shifts above E_F, then charge is pulled out of it. The magnetic moment of the ion depends on how the d-orbital is filled with electrons, but the precise filling is difficult to determine when only a limited energy range is experimentally accessible.

This is where a subtle phenomenon known as the Kondo effect proves useful. The Kondo effect (*10*) describes the process by which electrons from a surrounding substrate magnetically screen the spin of a magnetic ion. This effect is driven by an interaction between the localized spin of the ion and the itinerant spins of the substrate, and induces the magnetic ion to effectively "capture" an electron spin from the substrate and loosely bind it in a net-zero-spin configuration (that is, the two spins cancel). The signature of the new bound state is a narrow resonance (the Kondo resonance) that appears at E_F and whose width (the Kondo temperature) gives a measure of the captured spin's binding energy (*10*). Historically, this effect has been observed in bulk materials containing magnetic impurities because a change in the density of states at E_F can significantly affect bulk properties such as magnetization, specific heat, and conductivity. More recently, the Kondo effect has been

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