Human biology: an ever-expanding subject

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The fourth Wisconsin Symposium on Human Biology took place in Madison, Wisconsin, May 22–25, 2006, under beautiful Spring weather (which typically precedes the less enjoyable long, hot, humid Wisconsin summer). This symposium is held once every two or three years (the previous meeting was in 2003) and the series is shaping up as one of the most ambitious—and interesting—of multidisciplinary symposium programmes in the United States. The breadth of this particular meeting is indicated by its subtitle: ''Analysis & Synthesis, The Individual and the Environment, Robustness and Plasticity''. An explicit goal of the organisers is to promote provocative, multidisciplinary thinking within a university setting. The University of Wisconsin, with its distinguished and long history of research on and discoveries in basic biology generally and human health, more specifically, is a highly suitable university venue for this kind of intellectual venture. Nearly 50 years ago, C.P. Snow, in a lecture at the University of Cambridge, discussed the enormous gulf in understanding and communication between the humanities and the sciences, the problem of the ''two cultures''. Today, in biology alone, there are nearly comparably large splits between the different disciplines. The symposium series is, in effect, a bet that a comprehensive university can bring together highly specialized investigators to address shared problems from complementary angles, in an effective and insightful fashion.

Both the title and subtitle of the symposium inevitably prompt the question: just what precisely is ''human biology''? The short automatic answer is: ''biology that is relevant to human beings''. But this, as it transpires, is virtually *all* of biology *plus* all the cultural/social modes that impinge on this biology. In effect, the subject of ''human biology'' is virtually unbounded, unlike that of the biology of many simpler organisms, which themselves can be the focus of excellent symposia that make no reference to much of the multidimensional complexity of the biology of human beings.

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The program fully reflected this breadth and diversity of topic, ranging in level from the molecular to the cellular to the organismal Talks on some of the simpler organisms focussed on molecular events at the molecular scale. These ranged from viral life cycles (**John Yin**, University of Wisconsin), homeostasis in yeast phosphate metabolism (**Erin O'Shea**, Harvard), to gradients in early development of the fruit fly (**Naama Barkai**, The Weismann Institute). At the cellular level, there were talks on ''microfluidics'' in the governance of cell growth (**David Beebe**, University of Wisconsin) and the study of neural stem cells to probe basic cellular behaviour in neural growth and regeneration (**Clive Svendsen**, University of Wisconsin). At the most complex end of the spectrum, there were talks (to be described below) on human evolution, the nature of maternal effects on mammalian development, and the neurobiology of higher brain functions such as emotion, meditational states, and comprehension of music. Nor were technical topics neglected: important new advances in diagnostic methods, for humans and microbes, respectively, were described by **Charles Cantor** (Sequenom, Inc.) and **Ranga Sampath** (ISIS Pharmaceuticals).

To provide landmarks in this vast terrain, there were four plenary talks (one each day) that addressed large, central themes. All other presentations were grouped in separate subject-based sections, which ran in two concurrent streams. For the relatively rare individual whose interests are as broad as the symposium's range of subject matter, the dilemma was choosing which session of the two streams to go to at any one time.

In this report, we shall not attempt to mention and summarize every talk but concentrate on those that dealt directly with one or more aspects of the biology of human beings; we give our apologies to those whose talks are not mentioned here, for reasons of space and focus. The symposium website (http://www.union.wisc.edu/humanbiology/) gives the full set of abstracts and links to the speakers and organizers.

The keynote talk, opening the meeting, was given by **Michael Meany** (McGill University), whose subject was the variety of maternal effects and their long-lasting developmental sequelae in the offspring, particularly those involving maternal stress. He introduced the phenomenon of maternal environmental experience in animals with the example of *Daphnia* females exposed to the olfactory signals of predators; their offspring develop a special ''helmeted'' external armature.

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Comparable examples of such maternal/environmental developmental effects in ''lower'' animals are increasingly coming to light. He then described the data that elucidate how stress in mammalian mothers can lead to long-term neurological changes in their offspring. Specifically, the pups of stressed rat mothers who provide reduced maternal care in the first week of life of their offspring (reduced licking and grooming) show a long-term reduction in glucocorticoid receptor (GR) expression in the hippocampus. In effect, this leaves them in a permanent quasi-stressed state. The detailed analysis indicates the involvement of a specific cytosine-methylation event in the GR gene, which leads to this reduction in GR expression. Meaney's work tracks a long causal chain from a maternal behaviour to a highly-specific molecular change within a particular region of the infants' brains. One of the challenges will be to fill in many of the intermediate neurological steps between the initial maternal stress and the molecular outcome in the offspring.

Two talks explored just how much of interest lies at the neurological level alone in the investigation of brain states associated with experiential matters. These talks dealt specifically with emotion and learning, the area of research now designated as ''affective neuroscience''. **Elizabeth Phelps** (New York University) discussed fear-conditioning specifically and the regions of the brain associated with different kinds of learning in connection with fear or its absence. For ''neutral'' (non-fear inducing) events, the parahippocampus is involved in learning while the amygdala is not. For all fear-related responses, however, the amygdala is crucial, in both rats and humans, as shown by functional magnetic resonance imaging (FMRI), in which the amygdala ''lights up'' during fear responses. An intriguing finding is that some fear responses, e.g. to snakes or spiders, appear to be much more innate (''prepared'' is the term preferred by the field) in humans while other such responses are often learned, whether from verbal communication or from purely visual experiences. Various studies have shown that the involvement of fear in a learned response enhances the vividness of memories associated with the experience but does not enhance the accuracy. The interplay between emotional experience and cognitive outcome is clearly a complex one. **Richard Davidson** (University of Wisconsin) also examined affective (emotion-laden) experience and brain processing. Studies with brain imaging have pinpointed several cortical areas involved, and apparently required, in the cognitive processing of emotions. These cortical areas receive inputs from other brain areas, in particular the insula and the amygdala, for the consolidation of experience. Intriguingly, ''pure compassion'' in trained Buddhist monks can now also be connected with specific brain regions and activities, including, surprisingly, certain areas associated with motor responses. The latter finding may indicate a ''readiness to act'' associated with such compassionate states.

While the above talks tended to emphasize the value of a modules-centered approach to understanding brain function, it is clear that the human brain has remarkable capacities for inter-module substitution, the phenomenon of brain ''plasticity''. The work of **Paul Bach-y-Rita** (University of Wisconsin) involves the development of devices that can help overcome damaged sensory modalities by drawing upon other sensory abilities. In particular, his laboratory has developed a tongue sensor device that reports head tilt information to the brain to allow people with severe balance defects (up to 13 million in the United States alone) to re-establish stable balance.

The study of cognitive neuroscience is coming to address not only the fundamental understanding of the brain, but also to develop more effective approaches to human education. **Mark McDaniel** (Washington University St. Louis) described a series of experiments on information retention, illustrating the importance of active retrieval. The interactive session on Learning Science and the Science of Learning then explored ways in which new educational modes are being developed, involving cooperative learning and other strategies for active participation in one's education.

An interesting facet of brain function is the processing of musical inputs. As **Robert Zattore** (McGill University) pointed out, the making and perception of music provide a ''window'' into general aspects of human brain function, involving general cognitive functions together with unlimited combinations of constituent elements, rather like language. Music, in certain respects, is uniquely human yet ancient to our species. (The oldest known instruments date to 9000 BC but this is almost certainly a severe underestimate of the earliest date of music making in *Homo sapiens*.) His talk concentrated on brain imaging in normal and musically talented individuals, to identify special regions involved in musical perception; a key finding is that Henschi's gyrus is crucial for melodic discrimination. The sensing of ''wrong notes'' by both normal and musically-gifted people indicates that there is some inner set of ''rules'' for musical apprehension. **Dr. Isabelle Peretz** (University of Montreal) presented a complementary set of studies, dealing with individuals whose musical sense is impaired. The most severe musical perceptual deficit is termed ''congenital amusia'' and involves a greatly diminished processing of pitch-related information, which is processed predominantly in the right hemisphere. From brain scans, the defect appears not to be in the auditory cortex but in abnormal connectivity patterns in the frontal regions of the cortex, consistent with amusia being a cognitive-processing defect rather than a perceptual one. Tests with other living primates have indicated, so far, that none has even a capacity to sense or enjoy music remotely similar to that of the human.

Such comparative studies bear directly, of course, on the evolutionary origins of our species and, in the session devoted to human origins, two rather different views were presented.

Daniel Lieberman (Harvard University) presented a wide range of evidence that the capacity for long-distance running (as opposed to rapid sprints) is a uniquely human trait. The development of this trait could have taken place only in hot dry climates and, thus, probably in regions much like the African savannahs of today. Its presumed function was the running down of prey animals to exhaustion. Yet, this capacity involves considerably more than the evolution of the appropriate leg muscles; the evolution of numerous other traits, involving other musculature (the gluteus maximus, in particular), tendons, the brain, the skeleton and other features, would have been required. In effect, much co-evolution of anatomy and physiology was necessary for maximal development of this special human trait. **Svante Pääbo** (Institute of Evolutionary Anthropology, Leipzig) outlined his very different approach of using genomics to study human evolution. One identifies specific human traits, and presumptive key genes for these processes, such as the *FoxP2* gene, which has been implicated by various human pedigree studies as crucial for the acquisition of language, and then looks for informative selective changes in these genes by the appropriate molecular evolutionary tests. Pääbo described the comparison of Neanderthal DNA sequences with modern human sequences, to search for informative differences, in particular genes that have undergone various ''selective sweeps'' in the lineage leading to *H. sapiens*.

Human evolution has involved more, of course, than the development of unique abilities and physiologies. It has also been a story of continuing competitive and co-operative evolution with microbes. These interactions, furthermore, are a continuing feature of human existence. **Yoshihiro Kawaoka** (University of Wisconsin) discussed recent studies on avian 'flu and comparative studies of different viral strains in relationship to their sites of action in the human body and their pathogenesis. He outlined the evidence that initial infection of humans by the avian flu virus involves a small percentage of cells in the human lung that express the bird-specific viral receptor form. The small percentage of these cells constitutes a partial barrier to infection, but once initial infection of these cells has taken place, rare mutations can ensue to allow attack of cells bearing the human-specific viral receptors, leading to full-blown infection. These properties may be an important part of the explanation of the relatively inefficient spread of the bird virus to humans and its devastating effects when it has made the species jump. Kawaoka described the potentialities and pitfalls of current drug therapeutic regimes. **Teresa Compton** (University of Wisconsin and Novartis Institutes of Biomedical Research) described a much more prevalent virus in human populations, human cytomegalovirus (HCMV). This virus is estimated to be resident in 60–80% of the global human population, though in most cases it is silent. Nevertheless, it remains a potentially deadly pathogen; it is estimated that by the time an individual is 70, approximately 20% of the activity of the immune system is devoted to fighting this virus. The intricate nature of the viral-host arms race involving this virus was described as well as some infection-blocking strategies that are being developed.

A very different sort of microbe–human interaction, or rather set of such interactions, was described by **Margaret McFall-Ngai** (University of Wisconsin). She reviewed the evidence for the existence of extensive microbial ''consortia'' within animal bodies. Many of these microbes play beneficial physiological roles (or key developmental ones) and are thus symbionts, not merely passengers, let alone pathogens. A particularly interesting comparative biological aspect of this subject is that vertebrates seem to have much larger consortia than other animal groups. Yet, the existence of these large microbial consortia is a relatively recently established fact: their existence and composition was long covert because of the difficulty of culturing them. The advent of PCR and other molecular detection techniques has permitted estimates of the numbers of their constituents. Thanks to these techniques, we now know that, in the human oral cavity alone, there are at least 700 resident microbial species, and an even greater number of species in the gut. To date, more than 2600 different bacterial species have been identified as full-time residents of the human body. McFall-Ngai discussed the circumstantial evidence that it is the adaptive immunity system of vertebrates that has permitted the relative expansion of microbial consortia and that this system, in effect, manages a highly complex set of different ''ecosystems'' of different microbial species within the vertebrate body.

The intersection between the world of the human and the microbial biosphere came into focus unexpectedly in the session on Race, Genetics, and Disease. **Marcus Feldman** (Stanford University) summarized the evidence that markers of ancestry are far more informative in disease association than are markers of racial origin. Analyzing *Mycobacterium tuberculosae* in San Francisco, three major phylogenetic classes have been found. These different classes correlate with the different continental ancestries of the carrier individuals!

In studying complex biology in the human, a key question is whether model organisms can provide directly useful information for human biology. Genetic model organisms such as *C. elegans* allow comprehensive mutational analysis to identify the function of genes. **Cynthia Kenyon** (UCSF) used mutational analysis of longevity in this organism to identify insulin-like growth factor as an important player. In the session on sleep and circadian biology, **Chiara Cirelli** (University of Wisconsin) described a genetic screen in *Drosophila* in which mutations leading to short sleep duration were found in the ortholog to the mammalian potassium channel gene. The experimental mammals the mouse and the rat also provide mutational information on gene function. However, much of the genetic variation in human biology involves polymorphisms, not knockout mutations. Two different presentations

explored polymorphic variation in the mouse and the rat to detect players in the cognate human process. **Alan Attie** (University of Wisconsin) reported a polymorphism in the mouse gene *SorCS1* that affects the development of diabetes in obese animals. He is pursuing this candidate in human association studies. **Michael Gould** (University of Wisconsin), in collaboration with the group of **Bruce Ponder** (Cambridge Research Institute), has discovered a locus at which polymorphism affects risk for mammary cancer in both the rat and human. Are the polymorphisms ancient, pre-existing the divergence between murine species and primates? Or, like the major histocompatibility locus in mammals, is the shared region one at which polymorphism is frequent owing to mutation or selection?

The study of systems is proceeding through cluster analysis by the statistical methods employed in bioinformatics. **Eric Schadt** (Rosetta Inpharmatics/Merck) complements this analytic approach by testing predicted nodes in regulatory networks through mutational analysis in the mouse. With this approache, he demonstrated that the lipoprotein lipase gene *Lpl*1 functions as a regulatory node in the metabolic network associated with susceptibility to diabetes that is polymorphic in mice.

The symposium was concluded with a plenary lecture by **Dr. Jeremy Nicolson** (Imperial College London), whose wide-ranging talk brought all of the themes of the meeting together. He described what may be called a Global Systems Biology approach to show how the different ''-omics'' methodologies can be used to explore both the pathogenic microbe–human interactions and the symbiotic ones. The approaches include: ''metabolome'' analysis of human urine which, with its 37,000 known constituents, is a superb source of information about health and disease states, age, gender, etc.; investigations of the components of the ''super-organism'' (a term from Dr. Joshua Lederberg) that includes the human being (with nuclear, organelle and microbial consortia genomes) and the interactions of these components; new ways to carry out personalized medicine, based on human genotyping and pharmaco-metabonomics; and mouse experiments to explore relationships between metabolome and transcriptome interactions in various disease states—and much more!

If anyone attending the symposium had started with the presupposition that ''human biology'' is necessarily a rather limited corner of biology, Dr. Nicolson's talk alone would have refuted that idea. ''Human biology'' is the future of such a large part of biology as a whole, not simply because this is where much of the funding will be, for practical considerations of health and disease, but because it includes virtually all of the phenomena of interest in biology generally. One can anticipate that the Fifth Wisconsin Symposium on Human Biology will be as rich in interest, and in interdisciplinary surprises, as was the fourth.