

Working Group on
MIND, BRAIN, AND EDUCATION

The PONTIFICAL
ACADEMY
of SCIENCES

THE SESSION COMMEMORATING
THE 400th ANNIVERSARY OF THE
FOUNDATION OF THE PONTIFICAL
ACADEMY OF SCIENCES (1603-2003)

Working Group on
STEM CELL TECHNOLOGY
AND OTHER INNOVATIVE THERAPIES

CASINA PIUS IV, VATICAN GARDENS
7-11 NOVEMBER 2003



VATICAN CITY
2003

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***25th Anniversary
of the Pontificate
of Pope John Paul II***



400th Anniversary
*of the **Foundation** of the*
Pontifical Academy of Sciences
(1603-2003)

FOREWORD

I am delighted and honoured to present the forthcoming session commemorating the four-hundredth anniversary of the foundation of the Pontifical Academy of Sciences. As has already been communicated, the celebration proper will take place on Sunday, 9 November 2003, when Holy Mass will be celebrated at the Church of St. Stephen of the Abyssinians, presided over by His Eminence Cardinal Carlo M. Martini. Afterwards, a round table on the history of the Academy will be held at the headquarters of the Academy: Prof. Carlo Vinti (Perugia) will give a paper on 'Federico Cesi and the First Accademia dei Lincei'; Prof. Antonino Zichichi (PAS, Geneva/Bologna) will discuss the subject 'Galilei, Divine Man'; Prof. Andrea Riccardi (Roma III) will talk on 'The Restorations of Pius XI and John Paul II'; and the President of the Academy, Prof. Nicola Cabibbo, will reflect on 'The Meaning of the Pontifical Academy of Sciences Today'. In addition to the Academic body, experts and observers, thirty-eight internationally distinguished Academies have been invited to participate and over twenty presidents have already announced that they will be present.

I enclose the general programme of the session, which includes the working groups on 'Mind, Brain and Education' and 'Stem Cell Technology and Other Innovative Therapies', to be held respectively on 7-8 November 2003 and 10-11 November 2003. Both meetings will be able to rely on papers of very high quality, as will be evident from the abstracts.

It only remains for me to thank first and foremost the Holy Father John Paul II not only because on 16 October he attained the twenty-fifth year of an exceptional pontificate, but also because he has wanted during this year to offer the Academy the gift of the restoration of its splendid buildings. When that great Pontiff, Pope Pius XI, gave these buildings to the Pontifical Academy of Sciences in 1923, he was convinced that this 'jewel of art',¹ which had been inaugurated by Pius IV in 1591, was a most suitable place for the location of the Pontifical Academy of Sciences. Employing the famous Latin phrase *'est omen in loco'*, he observed that this Casina, in the centre of the Vatican Gardens, was a place of quiet, of 'mystical quiet'.² The quiet of this place also comes from its connections and contiguity with the cupola of St. Peter's Basilica, which contains the tomb of the Apostle Peter and where 'a supreme effort of art and science' brings thought 'nearer to the Creator', and with the Picture Gallery, the Archives, the Library, and the Museum of the Holy See, 'all a treasure of science, of art' from which 'science and art will be able for a long time to draw sustenance'.³

Naturally, the completion of the restoration has allowed Casina Pio IV not only to return to its former architectonic splendour, but has also improved its working facilities, particularly in the conference hall. Now we can really say that the Academicians who work in this Pontifical Academy will raise their minds to God through the contemplation of nature, the presence of art, the grace of St. Peter, and their own research and reflections, aided in this by the presence of state-of-the-art technology. All this corresponds to the definition of prayer offered by Thomas Aquinas, 'the raising of the mind to God' (*'elevatio mentis in Deum'*),⁴ that great saint whom His Holiness John Paul II declared *Doctor Humanitatis*.

I would also like to thank Cardinal Martini, Professor C. Vinti, A. Zichichi, A. Riccardi and President N. Cabibbo for the celebration of this fourth centenary. An expression of gratitude must also be extended to the organisers of the session, and in particular to A. Battro, K. Fischer, P. Léna and N. Le Douarin, T. Boon-Falleur, who have prepared meetings that will be of a level to match its tradition. I would also like to thank in particular Cardinal K. Lehmann who went to great lengths in order to be able to participate. Our gratitude and best wishes must also be expressed to all the participants, who in various ways will enrich this meeting.

✉ Marcelo Sánchez Sorondo

¹ The Pontifical Academy of Sciences, *Papal Addresses to the Pontifical Academy of Sciences 1917-2002 and to the Pontifical Academy of Social Sciences 1994-2002. Benedict XV, Pius XI, Pius XII, John XXIII, Paul VI, and John Paul II* (The Pontifical Academy of Sciences, Vatican City, 2003), p. 21.

² *Op. cit.*, p. 22.

³ *Loc. cit.*

⁴ *S. Th.*, II-II, 83, 13. Cf. Damasceno, *De fide orth.* 3:24.

GENERAL PROGRAMME

Working Group on 'Mind, Brain and Education'

The Session Commemorating the 400th Anniversary of the Foundation
of the Pontifical Academy of Sciences (1603-2003)

Working Group on 'Stem Cell Technology and Other Innovative Therapies'

Working Group on:

MIND, BRAIN AND EDUCATION
(7-8 November 2003)

Honorary President:

Prof. Rita Levi-Montalcini (PAS, Rome)

Coordinators:

Prof. Antonio M. Battro (PAS, Buenos Aires)

Prof. Kurt W. Fischer (Harvard)

Prof. Pierre J. Léna (PAS, Paris)

Friday, 7 November

9:00 Prof. Nicola Cabibbo (President)

Welcome

Prof. Antonio M. Battro (PAS, Buenos Aires)

Introduction

MIND, BRAIN AND EDUCATION: A NEW FIELD OF RESEARCH AND PRACTICE

Chair: Prof. Antonio M. Battro (PAS, Buenos Aires)

9:30 Prof. Kurt W. Fischer (Harvard)

Mind, Brain and Education: Developmental Cycles of Brain and Skill

10:10 Prof. Wolf J. Singer (PAS, Frankfurt)

Brain Development and Education

10:40 Discussion

11:00 Coffee Break

11:30 Dr. John T. Bruer (McDonnell Foundation, St Louis)

Scientific Bridges Between Brain, Mind and Education

12:10 Dr. Fernando Vidal (Max-Planck Institute, Berlin)

Brainhood and the Mind/Brain/Education Project

12:40 General Discussion

13:00 Lunch

NEUROPHYSIOLOGY AND COGNITION

Chair: Prof. Wolf J. Singer (PAS, Frankfurt)

15:00 Prof. Daniel J. Cardinali (Buenos Aires)
Chronoeducation: How the Biologic Clock Influences the Learning Process

15:40 Prof. Hideaki Koizumi (Hitachi, Saitama)
Developing the Brain: An Approach Towards Learning and Educational Sciences by Functional Imaging

16:20 Dr. Fiona Doetsch (Columbia)
The Origin of New Neurons: Stem Cells in the Adult Mammalian Brain

17:00 Coffee Break

17:30 Prof. Maryanne Wolf (Tufts)
A Triptych of the Reading Brain: Evolution, Development, Pathology and its Intervention

18:10 Dr. Robert J. White (PAS, Cleveland)
The Isolated Brain

18:50 General Discussion

19:00 Dinner

Saturday, 8 November

Chair: Prof. Pierre J. Léna (PAS, Paris)

9:00 Dr. Stanislas Dehaene (Inst. National de la Santé, Orsay)
Pre-emption of Cortical Circuits by Calculation and Language: The Hypothesis of a Cultural 'Neuronal Recycling' Process

9:40 Prof. Paul van Geert (Groningen)
Dynamical Models and the Assessment of Individual Learning and Development

10:20 Prof. Michael Posner (Oregon)
Brain Mechanisms and Learning of High Level Skills

11:00 Coffee Break

11:30 Prof. Jürgen Mittelstrass (PAS, Konstanz)
Mind, Brain and Consciousness

12:10 General Discussion

13:00 Lunch

BRAIN AND LANGUAGE

Chair: Prof. Kurt W. Fischer (Harvard)

15:00 Prof. Laura-Ann Petitto (Dartmouth)

Revolutions in Brain, Language, and Education: Examples from Spoken Language and Silent Languages on the Hands

15:40 Prof. Eraldo Paulesu (Milano-Bicocca)

Language, Bilingualism and Bilingual Education

16:20 Prof. Usha Goswami (Cambridge, UK)

Reading and the Brain: A Cross Language Analysis

17:00 Coffee Break

17:30 Antonio M. Battro, Kurt W. Fischer, Juliana Paré-Blagojev (Los Alamos)

The 'International Mind, Brain and Education Society' and the 'MindBrain and Education' Journal

18:00 The Presidents of the Academies and the Participants are kindly invited to discuss and join these initiatives

18:30 Final Discussion

19:15 Guided visit to the Vatican Museums (Apollo, Laocoon, Belvedere Torso)

**THE SESSION COMMEMORATING THE 400TH ANNIVERSARY
OF THE FOUNDATION OF THE PONTIFICAL ACADEMY OF SCIENCES (1603-2003)**

Sunday, 9 November

9:30 Holy Mass celebrated by His Eminence Card. Prof. Carlo M. Martini, Church of St. Stephen of the Abyssinians (Vatican City)

10:45 Round Table on the *History of the Academy*.

– Prof. Carlo Vinti (Perugia)

Federico Cesi, the First Accademia dei Lincei and the Moral and Methodological Commitment of the Researcher

- Prof. Antonino Zichichi (PAS, Geneva - Bologna)
Galilei, Divine Man

- Prof. Andrea Riccardi (Roma III)
The Restorations of Pius XI and John Paul II

11:45 Coffee Break

12:00 Prof. Nicola Cabibbo (President of the Academy, Rome 'La Sapienza')
The Meaning of the Pontifical Academy of Sciences Today

12:45 Lunch at the Academy

15:15 Guided visit to the Vatican Museums (Sistine Chapel)

Working Group on:
STEM CELL TECHNOLOGY AND OTHER INNOVATIVE THERAPIES
(10-11 November 2003)

Organising Committee: N. Le Douarin (PAS, Paris), T. Boon-Falleur (PAS, Brussels)

Monday, 10 November

9:00 Prof. Nicole Le Douarin (PAS, Paris)
Introduction

9:30 Card. Karl Lehmann (Mainz, President of the Bishops' Conference)
Human Rights and Bioethics

10:30 Prof. Irving Weissmann (Stanford)
Stem Cells: Overview

11:30 Coffee Break

12:00 Prof. Ronald McKay (Nat. Inst. Neurological Disorder and Stroke, Bethesda)
Comparing the Properties of Embryonic, Fetal and Adult Stem Cells

13:00 Lunch

14:30 Prof. Azim Surani (Cambridge, UK)
Germ Cells: The Eternal Link Between Generations

15.30 Prof. Helen Blau (Stanford)
Repair of Adult Tissues by Adult Bone Marrow Derived Stem Cells

16:30 Coffee Break

17:00 Prof. Rudolf Jaenisch (MIT, Cambridge)
Nuclear Cloning and Embryonic Stem Cells

18:00 Prof. Ann McLaren (Cambridge, UK), Chairperson
General Discussion

Tuesday, 11 November

9:00 Prof. Thierry Boon-Falleur (PAS, Brussels)
Therapeutic Vaccination of Cancer Patients

10:00 Prof. Alain Fischer (INSERM, Paris)
Gene Transfer in Hematopoietic Stem Cells: Perspectives, Results and Problems

11:00 Coffee Break

11:30 Prof. François Sigaux (INSERM, Paris)
From Genes to Therapy

12:30 Lunch

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Working Group on

MIND, BRAIN AND EDUCATION

The Pontifical Academy of Sciences is celebrating the 400th anniversary of its foundation at the Vatican by Pope Clement VII and Prince Federico Cesi with the name Linceorum Academia (Academy of the Lynxes). Galileo Galilei was the most prestigious member of this academy, the oldest of Europe (1603) in the mathematical and experimental sciences. Today the Academy has eighty members from twenty-six countries. Some thirty of them have Nobel Prizes. The meetings are held at the Casina Pio IV in the Vatican Gardens, a famous palace of the Renaissance.

This meeting on Mind, Brain and Education was organized by Antonio M. Battro (Academia Nacional de Educación, Argentina), Kurt W. Fischer (Harvard University Graduate School of Education) and Pierre Léna (Université Denis Diderot, Paris) with the purpose of joining the gaping seams in the patchwork quilt that connects neuroscience findings with educationally relevant problems. Rita Levi Montalcini (Nobel Prize winner) is the honorary president of this meeting.

In the current Age of Biology, society is looking to neuroscience, genetics, and cognitive science to inform and improve education. To create better research and practice, we must build a reciprocal relationship of educational practice with research on learning and development, analogous to the relationship between biology and medicine. In this relationship, research informs practice, and simultaneously practice informs research.

The workshop on Mind, Brain and Education will search for convergent trends in the fields of Epistemology (Bruer, Mittelstrass), History (Vidal), Language (Paulesu, Petitto), Mathematics (Dehaene), Brain images (Koizumi), Neurobiology (Doetsch, Singer, White), Reading (Goswami, Wolf), Dynamical models (Fischer, van Geert) and Chronobiology (Cardinali). The results of this workshop will be published in a book, and a new International Mind, Brain and Education Society (IMBES) and a Journal, (Battro, Fischer & Paré-Blagoev) will be launched at the end of the sessions.

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ABSTRACTS

SCIENTIFIC BRIDGES BETWEEN BRAIN, MIND AND EDUCATION

JOHN T. BRUER

I have been critical of how neuroscience research findings are being used to support recommendations for educational policy and practice advanced by policy advocates, educators, and the media. However, these popular explanations could not have gained prominence if they had not been endorsed either actively or passively by a cadre of neuroscientists. There is a tendency among neuroscientists to accept that findings at the cellular or molecular level (e.g. developmental synaptogenesis) can explain some gross, unanalyzed observed behavior (e.g. ease and efficiency of learning) as in 'children learn best when synaptic densities are highest'. This willingness to extrapolate glosses over how little we know about synaptic change and learning and ignores entirely what psychological research tells us about learning. Facile attempts to link brain, mind and learning tend to overlook the contribution an intermediate level theory – a level of theorizing between brain and behavior – must make to such a research program. Cognitive neuroscientists assume that cognitive analyses and models provide an appropriate intermediate-level theory of mind. On this assumption, how might cognitive neuroscience contribute to an applied science of learning? Are there other intermediate level theories? What are the prospects for neuro-social psychology, neuro-attachment theory, or neuro-economics?

* * *

CHRONOEDUCATION: HOW THE BIOLOGIC CLOCK INFLUENCES THE LEARNING PROCESS

DANIEL P. CARDINALI

Diurnal, nocturnal or seasonal modes of behavior are not passive responses to changes in the environment. Rather, they are generated by an endogenous circadian pacemaker, entrained by a few environmental cues like light-dark cycles. Circadian clock mechanisms involve periodic gene expression, synchronized by a hierarchically superior structure located in mammals in the hypothalamic suprachiasmatic nuclei. Cycles of sleep and wakefulness are the most conspicuous circadian rhythms. Sleep is a behavioral state defined by: (i) characteristic relaxation of posture; (ii) raised sensory thresholds; (iii) distinctive electroencephalographic signs. Two main, though not mutually exclusive, hypotheses have been predominant in interpreting sleep: (i) sleep is restorative for brain metabolism; (ii) sleep serves memory consolidation and the learning process. Since modern humans use artificial light to extend their period of wakefulness and activity into the evening hours, they adhere to a short night sleep schedule with a highly consolidated and efficient sleep. As shown by studies in artificial long nights, modern humans may be sleep-deprived. In this presentation I will discuss the physiological consequences of such sleep deprivation with a focus in the learning processes.

PRE-EMPTION OF CORTICAL CIRCUITS BY CALCULATION AND LANGUAGE: THE HYPOTHESIS OF A CULTURAL 'NEURONAL RECYCLING' PROCESS

STANISLAS DEHAENE

Contrary to other primates, humans have a remarkable ability to invent symbols systems such as Arabic numerals or the alphabet. Those inventions are too recent to rely on a dedicated brain substrate acquired during evolution. How, then, are they implemented in the human brain?

My colleagues and I use brain imaging and neuropsychological methods to probe the neural bases of arithmetic and reading abilities. Our results indicate that humans and other primates share a non-verbal sense of approximate numerosity, which has a long evolutionary history and a specific cerebral substrate in the bilateral horizontal segment of the intraparietal sulci (IPS). Habituation and parametric fMRI experiments support the hypothesis that the parameter of numerosity is represented by populations of 'numerosity detecting' neurons, each tuned to a particular numerosity. Regions sensitivity to numerosity are distributed and overlapping with those coding for other quantitative parameters such as size and brightness, amidst other parietal lobe circuits for sensori-motor operations of grasping, pointing, attention and eye movements.

During calculation with Arabic symbols, humans quickly access the numerosity representation, and they rely on this approximate numerosity code for operations of comparison and approximate calculation. Thus, an evolutionary ancient representation is put to use for the purpose of recent symbolic manipulations, including elaborate mathematical ones. Similarly, my colleagues and I have shown that the human cultural ability to read makes use of the ventral inferotemporal object recognition system. During the acquisition of reading, part of this system, at a reproducible location within the left occipito-temporal sulcus, becomes highly specialized for the visual operations underlying case-invariant letter and word recognition. This 'visual word form system' should not be considered as a 'module' for visual word recognition, but rather as a population of neurons, distributed and overlapping with other populations involved in face and object recognition, which becomes progressively attuned to the reading process.

As a generalization of those two examples, I tentatively propose that our human ability to learn cultural objects relies on a cultural 'neuronal recycling' process whereby those novel objects invade cortical territories initially devoted to distinct but close functions. According to this view, our evolutionary history, and therefore our genetic organization, specifies a plastic cerebral architecture that delimits a space of learnable cultural objects. Contrary to some social scientists that consider learning as an open-ended source of unbounded cultural variation, this view predicts that the human abilities for cultural invention, although extensive, are eventually limited by the envelope of possibilities inherent in our brain circuits. It also implies that the difficulty of learning certain concepts or techniques may be explained by the amount of transformation that separates the initial, evolutionarily inherited function and the new, culturally acquired one. This view therefore has implications for mathematics and reading education.

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THE ORIGIN OF NEW NEURONS: STEM CELLS IN THE ADULT MAMMALIAN BRAIN

FIONA DOETSCH

Stem cells residing in germinal regions in the adult brain continuously generate large numbers of neurons, which become integrated into neural circuits. In mammals, new neurons are incorporated into areas important for olfaction and for memory formation. The addition of thousands of neurons each day provides a powerful means of sculpting brain circuitry and may play a role in learning and memory formation. Although the functional consequences of adult neurogenesis are not yet understood, much has been learned about their cellular lineage. Adult neurogenesis occurs in specialized niches near the brain ventricles and in the hippocampus. Surprisingly, the stem cells for *in vivo* adult neurogenesis are a subset of astrocytes, glial cells commonly associated with support functions in the nervous system. Stem cells in the subventricular zone, an extensive germinal region in the adult brain lying next to the lateral ventricles, generate neurons destined for the olfactory bulb via rapidly dividing intermediate transit amplifying cells. The newly generated neurons then migrate as chains along a network of pathways to reach the olfactory bulb where they differentiate into inhibitory neurons. Interestingly, stem cell potential is not only restricted to the *in vivo* stem cells; transit amplifying cells can also act as stem cells when stimulated with growth factors. The identification of the *in vivo* stem cells as astrocytes raises the exciting possibility that other brain astrocytes may be latent stem cells. How stem cells and adult neurogenesis affect brain function and their role in plasticity both under normal conditions and after injury are crucial unresolved issues.

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MIND, BRAIN AND EDUCATION: DEVELOPMENTAL CYCLES OF BRAIN AND SKILL

KURT W. FISCHER

In the current Age of Biology, society is looking to neuroscience, genetics, and cognitive science to inform and improve education. Scientists and scholars need to take responsibility for building strong connections of mind, brain and education to provide usable research-based knowledge for education. Many of the efforts to relate biology to education have been at best useless and at worst pernicious, such as most of what is called 'brain-based education'. To create better research and practice, we must build a reciprocal relationship between edu-

cational practice and research on learning and development, analogous to the relationship between biology and medicine. In this relationship, research informs practice, and simultaneously practice informs research.

An example of both the promise and the pitfalls of this relationship is research on cycles of development of cognition and brain, which shows important stage-like properties. Children and adolescents demonstrate clear spurts in optimal performance at certain age intervals for skills with a specifiable kind of structure. For example, such spurts and other discontinuities occur at approximately ages 3½-4½, 5-7, 10-12, 14-16, and 19-21 years. These spurts seem to reflect a dynamic *upper limit* on the complexity of skills that a person can control, while most ordinary performance below the upper limit evidences no spurts.

Similarly, research on cortical activity shows strong spurts and other discontinuities in energy and coherence of cortical electroencephalogram (EEG) at similar ages, suggesting straightforward connections of brain and cognitive development. We have proposed an explicit model of how the cortical changes relate to the cognitive changes.

Scientists and practitioners alike tend to move quickly from these correlations and this model to implications for education. Indeed, we expect that eventually the research will lead to important educational implications. However, the first discoveries of related growth spurts highlight the dangers of premature jumps to conclusions. In the 1980s several American biologists were jumping from evidence of head-growth spurts to conclusions about how learning occurs in school children, making recommendations to school boards and teachers without any evidence that assessed actual learning. Usable research-based knowledge will come from relating brain-activity measures to analysis of children's learning in school and the rest of everyday life.

The key to creating usable knowledge in mind, brain and education is not to simply wait for neuroscience to 'mature' but to be proactive. Building a new kind of relationship requires researchers and practitioners who are knowledgeable about biology, cognitive science, and education and so can join research and educational practice in active collaboration.

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MIND, BRAIN AND EDUCATION: A DYNAMIC AND COMPLEXITY APPROACH

PAUL VAN GEERT

Mind, brain and education form a complex dynamic system. A complex system consists of a great number of components that interact with each other over time and by doing so create the system's integrity and pattern of change. A complex system such as the Mind-Brain-Education system has a number of striking characteristics that are in fact the hallmarks of its complexity. I will argue that this system can only be understood if these characteristic features are explicitly taken into account.

A first striking feature is the simultaneous occurrence of (seemingly) paradoxical properties, which amounts to a kind of superposition of (seemingly) mutually exclusive features. An example of this superposition is the relationship between cause and effect in a developmental or educational process: a developmental event is at the same time its own cause and its own effect. This phenomenon becomes understandable as soon as we realize that it is based on recursive or iterative processes, in which the former step is the cause and condition of the next step. It can be described and understood by means of dynamic systems models, in which the recursive nature of the process is explicitly taken into account. Another example of this (apparent) superposition is the question of genes versus environment in development or the question of brain versus mind or behavior. The complexity of the way in which genes and environment interact excludes simple additive solutions, as if genes explain $x\%$ and environment $1-x\%$ of the variance. Since both genes and environment are organized in the form of a developmental process, where one has an effect on the shape of the other and vice versa, it makes sense to view both, to a certain extent, as each others' product and cause at

the same time. A similar point can be made about the search for biological (neurological) causes of child clinical conditions, such as hyperactivity (ADHD), autism, specific language impairment and so forth. In order to make further progress towards understanding these problems, they must be formulated in the framework of recursive dynamic processes. Modeling such processes will also help us understand additional features such as non-linearity, discontinuity, variability and so forth.

A second striking feature of complex systems is their multi-layered character. The components distinguished at one level of description can be indistinguishable at another. The processes take place on different time scales. These different scales and layers are not just trivial descriptive distinctions. They are characterized by their own dynamics and require the interaction with the dynamics of other layers and scales. Changes at the level of the historical time scale deeply affect the pattern of ontogenesis, but the pattern of ontogenesis on the other hand is a major force in the dynamics of historical and evolutionary time. The layers and scales do not amount to static distinctions: they are of an inherently dynamic nature. For instance, if we think about a property such as intelligence, or a process such as problem solving, it is difficult if not impossible to draw a sharp line between the factors 'inside' and those 'outside' the subject that make intelligence or problems solving possible. This difficulty is related to the so-called Situatedness or the distributed nature of what we are used to call psychological properties. These properties are in fact distributed over the person and the person's environment and are dynamically assembled, in variable ways, as those psychological properties emerge in concrete actions and situations.

This dynamic view of complexity is of little scientific use if it only serves to make our image of the world more obscure. An important question is how this view is going to help us do better research in the field of human development and education. The phenomena that developmental and educational psychologists are interested in are for the most part complex themselves, are characterized by inherent vagueness and fuzziness and are difficult to observe. The standard solution of attributing part of the complexity to measurement error and solve this error by measuring over many independently sampled individuals is not going to work if we aim towards understanding the dynamics of the developmental and educational process. On the other hand, direct observation of the dynamics of development and education sometimes poses insurmountable methodological and ethical problems. I will discuss a limited number of approaches that will help us focus on the dynamics, without being unrealistic about our scientific possibilities. One approach is the use of dynamic modeling as a conceptual and exploratory tool. All too often, models are seen as the endpoint of scientific inquiry, whereas they should in fact be used to guide us through the research process, especially in the initial stages. Another approach is to shift our focus from estimations of fixed and 'crisp' psychological properties (traits, true scores, etc.) to dynamic features. An example of such a dynamic feature is intra-individual variability, which may provide information about continuous versus discontinuous change and about the nature of the underlying generators of behavior. Finally, although cross-sectional research cannot provide information about individual dynamic patterns of change, it may nevertheless contain information about such dynamic patterns, if attention is shifted from the search for central tendencies to the search for inter-individual differences, context-dependency etc.

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READING AND THE BRAIN: A CROSS LANGUAGE ANALYSIS

USHA GOSWAMI

In this paper, I will provide a theoretical overview at the cognitive level of reading acquisition and developmental dyslexia across languages. Phonological awareness is a strong predictor of reading development, and develops at three linguistic levels. These are the levels of the syllable, the rhyme and the phoneme. I will describe developmental studies showing that syllabic rep-

resentation is basic to many languages, and that children's ability to recognise syllables and rhymes *precedes* learning a particular spelling system. I will argue that this developmental view can readily explain cross-language differences in reading acquisition and in the manifestation of developmental dyslexia. I will then suggest that some of the neural processes underpinning language acquisition are disrupted in developmental dyslexia, particularly basic auditory processes. This leads to deficits in the development of phonological representation before literacy is acquired, leading to characteristic and persistent problems in acquiring literacy. I will then describe some new studies aimed at pinpointing the source of the auditory deficit, using behavioural and ERP techniques. Rather than focusing research on the basic auditory processes required for phoneme perception, I argue that changing the focus to processes yielding rhyme and rhythm perception may be more fruitful.

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MIND, BRAIN AND CONSCIOUSNESS

JÜRGEN MITTELSTRASS

Philosophy should not try to solve problems that science can do better at. Today, such problems would appear to include the relationship between mind, brain and consciousness. What was once a philosophical problem, above all the doctrine of Cartesian Mind-Body Dualism, has now become a research programme in biology and neurophysiology. But that does not have to be the last word on the matter. For the concepts of mind and consciousness cannot be reduced to natural scientific terms without residue. This is in part the consequence of translation difficulties between the conceptual systems of philosophy, psychology and neurophysiology. But it derives as well from our self-understanding, which is also expressed in terms of consciousness and self-consciousness. From a methodological point of view, this state of affairs is connected with monistically and dualistically oriented analyses. After a few short historical remarks, these analyses will be described. I will then attempt to steer a middle course between the dilemma posed by two apparently incompatible positions – thus a cooperative road to be taken by the philosophical and scientific research programmes. This will concern above all the problem of self-consciousness.

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INTRODUCING THE MINDBRAIN AND EDUCATION JOURNAL

JULIANA PARÉ-BLAGOEV

The creation of the International Mind, Brain and Education Society will be a significant step forward in fostering meaningful interactions between cognitive science, neuroscience and educational practice. This Society represents the body of collective knowledge between these intersecting fields, and the new journal MindBrain and Education gives voice to this body. We intend this journal for a wide range of researchers in neuroscience, psychology and education as well as practicing teachers with a broad interest in the biological and behavioral bases of learning and development. In keeping with the nature of this developing field, MB&E will have an interdisciplinary character; articles will be written for an educated, but not highly technical audience. A focus of the journal is on synthesizing commentary and cross-disciplinary analysis of relevant research and theory. In addition to theory and review papers, appropriate original research articles exploring falsifiable claims regarding the biological or cognitive bases of educationally relevant behaviors and abilities are to be included.

The editorial policy of the Journal is non-ideological and multi-disciplinary. MB&E will welcome work from geneticists, cognitive neuroscientists, developmental psychologists, sociologists, anthropologists, education researchers, and other scholars without, it is hoped, being captured by any one group. The highly interdisciplinary and international makeup of MB&E's editorial board assures representation of a wide range of disciplines, research directions, and, particularly important in education research, cultural differences and theoretical assumptions.

This journal joins the gaping seams between the patchwork quilt of neuroscience findings and educationally relevant problems. Work in mind, brain and education does not involve simply cutting away an appealing scientific finding and fitting it more or less to classroom practices. What is crucial in this research is a reciprocal relationship in which education informs biological research as much as biology informs educational research and practice. For example, reading a string of words in a reaction time study in an fMRI magnet is distant from reading words in a textbook. Laboratory research plays an important role in analyzing fundamental processes, but research in the settings of practice is key to translating basic findings to appropriate application. Educational relevance can also provide a theoretical framework helpful for interpreting basic findings. For example, psychophysics research on subtle auditory deficits becomes more broadly meaningful when connected to proficiency in phonemic awareness, a key skill in reading.

The connection of education to the biological and cognitive sciences will not wait for neuroscience to analyze mechanisms of mind-brain relationship. Educators, scientists, and laypersons are calling for such connections in many ways, some productive, and others relatively unsupported with predictably poor results. Medicine did not wait for biochemistry to mature before connecting to biology. Education will not wait for neuroscience and cognitive science to mature either. This journal will be a clearinghouse, and itself provide an impetus for scientifically solid, educationally relevant research connecting MindBrain and Education.

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REVOLUTIONS IN BRAIN, LANGUAGE, AND EDUCATION: EXAMPLES FROM SPOKEN LANGUAGE AND SILENT LANGUAGES ON THE HANDS

LAURA-ANN PETITTO

For thousands of years, our species has pondered the nature of Language. The fundamental question has been what are we humans born with, and what is in the environment, which makes possible the remarkable feat of acquiring Language? Traditional answers have assumed that the development of the mechanisms for speaking and hearing neurologically determine the time course, structure, and content of very early language acquisition. Indeed, the view has been that language acquisition begins and develops because the capacity for producing and perceiving speech *sounds* begins and develops. Three decades of studies from my laboratory, however, have yielded discoveries demonstrating that this long-cherished view is wrong. Rather than language acquisition being driven by our capacity to speak and hear sounds, it is driven by our capacity to detect, discern and generate highly specific *patterns* that form the core of human Language. Our comparative studies of hearing babies acquiring spoken languages and deaf babies acquiring signed languages have revealed that their developmental time course, grammatical structures, and semantic content are the same [1]. Even profoundly deaf babies babble just like hearing babies, but do so on their hands [2], and bilingual signing-speaking children acquire each of their languages on the identical time course as monolingual children [3]. Furthermore, using PET/MRI brain scanning techniques, we discovered that the brains of deaf adults showed robust activation in specific cortical tissue, called the Planum Temporale (PT, a region in the Superior Temporal Gyrus), which has been thought to be unimodal sound tissue for the past 125 years. Like hearing people processing

sound-based phonetic-syllabic units, profoundly deaf brains process silent phonetic-syllabic units formed on the hands in signed languages in the PT [4]. In our recent morphometry study of cerebral tissue volumes, we found that this PT 'sound' tissue had highly similar gray- and white-matter volumes in profoundly deaf and hearing brains, and, like hearing brains, deaf brains showed a greater PT volume in the left hemisphere over the right [5]. Without the benefit of sound input, this ostensible 'sound' tissue is nonetheless 'alive'. This is so because the tissue is not dedicated to sound but to performing specific temporal and distributional analyses unique to Language structure and can do its job whether using the silent patterned hands of a natural signed language or speech. Our studies have further demonstrated that left hemisphere specialization for language governs the *production* of very young babies' linguistic vocal productions from early life (such as 'babbling') over all other vocal/mouth productions [6] and our latest Optical Topography (Near-Infra Red Spectroscopy) studies of the brains of young babies have also demonstrated that PT tissue is robustly active when babies *perceive* linguistic stimuli as compared to other non-linguistic stimuli. Taken together, this research points to the existence of select tissue in the human brain that helps babies learn language. The human brain possesses specialized tissue dedicated to processing specific maximally-contrasting temporal patterns (and their distributions) relevant to specific aspects of the structure of natural Language (e.g., phonetic-syllabic units) – a pattern sensitivity that is both distinct from a specific modality such as sound and highly unmodifiable in so far as languages in radically different modalities will be processed in the same loci. At the same time, the expression of this pattern sensitivity is highly modifiable and can recruit multiple pathways (hands or tongue) as a result of the modality of language input. Thus, human language acquisition entails both specialized tissue and tissue that becomes specialized over time. One new implication here is that language modality, be it spoken or signed, is so plastic that it only becomes neurologically set through neurogenetic processes *after* birth.

Educational Neuroscience. Neuroscientific studies like those identified here have yielded an explosion in our understanding of the brain's stunning ability to organize itself in early childhood. We now know the crucial time periods in child development during which neural plasticity (neural reorganization) is at its peak, and the key factors of the child's environment upon which normal emotional, cognitive, and linguistic growth depends. Crucially, they teach us precisely what types of experiences all children must have in order to achieve optimal growth and development. Such neuroscience studies have already begun to revolutionize our methods of learning and teaching in Education. For example, our understanding of the role and developmental time course of the PT tissue in early normal language development has taught us that it figures prominently in atypical language disorders, such as Dyslexia, and that it lies at the heart of many young children's reading disorders. Armed both with this knowledge and with contemporary neuroscience technology, we hope to identify normal and dysfunctional PT processing in very young babies thereby providing the earliest predictor of children at risk for language disorders even before they utter their first words. Currently, language disorders are not diagnosed until a child is several years old. This, in turn, will permit early invention and remediation programs to be developed that target phonological enhancement at a time in a child's development when he/she needs it most. Moreover, we now have a clear understanding of the role that PT tissue plays in making possible early childhood bilingual language acquisition. We know that PT tissue develops on a strict maturational timetable and that early bilingual language exposure is *best* for children to achieve full native linguistic mastery in each language. Yet prevailing educational policy and practice flies in the face of these biological facts by withholding early exposure on the erroneous opinion that dual language exposure may cause language delay and confusion. It does not – and, based on neuroscience studies of bilingual processing, such educational practice is now undergoing slow but steady revision. Indeed, this new approach, Educational Neuroscience, with its mutual understanding of biological and environmental factors that make human development possible, is shedding new light on when, how, and what to teach children, and how children can best be guided to conceptual change, insight, and discovery.

For reprints and more information, see Prof. Petitto's Research Web site:

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BRAIN MECHANISMS AND LEARNING OF HIGH LEVEL SKILLS

MICHAEL I. POSNER *and* MARY K. ROTHBART

Progress in neuroimaging and in sequencing the human genome make it possible to think about high level cognitive skills in terms of experiential and genetic factors that shape development of appropriate underlying neural networks. We have carried out an extensive series of investigations of an attentional network related to self regulation of cognition and emotion. This network involves a specific anatomy that includes midline and lateral frontal areas. We have used a number of conflict tasks shown to activate these brain areas to study the development of the network from 2.5 to 7 years of age. Individual differences in the development of this network have been related to parental reports of ability of children to regulate their behavior, to delay reward and to activate brain areas in high level skills. In adolescents these individual differences predict the propensity for anti social

behavior. We have found alleles of two genes that show a relationship to individual efficiency in performance and to the degree of activation of a node of this network in the anterior cingulate gyrus. We are now studying whether specific training experiences can influence the development of this network in four year old children. Our preliminary results give evidence of improvement with training and indicate that children with poor attentional skills can benefit the most from such training.

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BRAIN DEVELOPMENT AND EDUCATION

WOLF J. SINGER

Human babies are born with very immature brains. At the time of birth the full set of neurons is already present – but most of them, especially in the cerebral cortex, are still undifferentiated and unconnected. Outgrowth of connections and synapse formation continue until puberty in certain brain regions, and these differentiation processes occur in two major waves: One during the first years after birth, and the second prior to puberty. The fascinating aspect of these developmental processes is that they are influenced to a large extent by neuronal activity. Cells tend to wire together if they fire together, and cells exhibiting mainly uncorrelated activity lose their interconnections. As neuronal activity is to a large extent modulated by sensory signals and interactions of the organism with its environment this implies that the fine tuning of the brain's architecture depends on experience and environmental factors. These epigenetic shaping processes occur at different times and different brain regions and are irreversible, once the respective time windows close. These facts emphasize the extraordinary importance of environmental influences and education on the development of the functional architecture of the brain.

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BRAINHOOD AND THE MIND/BRAIN/EDUCATION PROJECT

FERNANDO VIDAL

Since *personhood* is the quality or condition of being an individual person, I would like to propose the term *brainhood* to name the quality or condition of being a brain. This property defines the 'cerebral subject' that emerged in the second half of the twentieth century. The 'cerebral subject' presupposes both *homo cerebialis* (M. Hagner) and the 'neuronal man' (J.-P. Changeux), but is not coextensive with them. The notion of *homo cerebialis* highlights the transformation of the seat of the soul into the organ of the self; 'neuronal man' underlines the material foundations of personal identity. The idea of a 'cerebral subject' defined by the ontological property of brainhood is broader in that it designates an anthropological figure – the human being *as brain* – with a great diversity of social inscriptions, embodiments and crystallisations, both inside and outside the philosophical, psychological and neuroscientific fields.

This paper explores some aspects of the historical development of brainhood, as background to the conditions of possibility for the emergence of Mind/Brain/Education. This new area of research and practice could obviously not exist without major advances in the scientific knowledge of the brain structure and functioning, including the development of various techniques of visualisation and neuronal and neurocognitive intervention. Yet it also rests on certain assumptions about the human being, and especially about the relationship between 'being human' and 'having a brain'. In seeking to conceptualize the relation between mind and brain, the various forms of neurophilosophy and philosophy of mind (more or less 'emergentist' or reductionistic) share with the neurosciences at least one belief: that the brain, whole or in part, is the only bod-

ily organ truly indispensable for the existence of a human self and for defining individuality. Indeed, contrary to what occurs in all other cases of organ transplantation or body modification, it is assumed that if the brain of person A is transplanted into the body of person B, it is not B who receives a new organ, but A who gains a new body.

Far from being the inherently necessary *result* of neuroscientific progress, such cerebralisation (or, better, corticalisation) of personhood and individual identity is a historically contingent *assumption* of the modern neurosciences. In the course of the eighteenth century, at the crossroads of philosophy, psychology, medicine and theology, the brain became not only the seat of personal identity, but, more radically, the only bodily part essential to the self – the only organ that we need to have, and that has to be intrinsically ‘our own’ in order for us to be ourselves. The development of neurology and the neurosciences in the nineteenth and twentieth century crucially reinforced this early view. In the chapter on personal identity added to the second edition of his *Essay concerning human understanding* (1694), the English philosopher John Locke imagined puzzle-cases. He asked, for example, what happens if the soul of a prince turns up in the body of a cobbler, or if consciousness is located in the little finger and this finger is separated from the rest of the body. These fictions were for him springboards to discuss personal identity, and to support his definition of identity as a continuity of consciousness and memory. In the 1960s, philosophers of the analytic anglo-american tradition revived the Lockian approach. They too used puzzle-cases as an analytical and argumentative strategy. Now, however, the paradoxes concerned the brain (experiments, transplants, extra-bodily conservation). This usage became so widespread that it seemed virtually impossible to discuss personal identity without having recourse to cerebral surgical fictions.

The rise of philosophical brain-fictions coincided chronologically with the increasing importance of brain research. Symbolically, institutionally and financially, the latter was signalled not only by the development of the neurosciences as a network of autonomous fields, but also by the establishment of the International Brain Research Organization in 1960, the proclamation in 1990 of the Decade of the Brain, and the claim that the twenty-first century is going to be the century of the brain. The Mind/Brain/Education project might become an emblematic enterprise of such a century. Putting aside for a moment the hopes it legitimately raises, this paper aims to contribute some elements for placing it in a historical and anthropological perspective.

* * *

THE ISOLATED BRAIN

ROBERT J. WHITE

This presentation describes the unique findings resulting from studies of brain functioning involving an isolated subhuman brain preparation maintained in a living state employing cross circulation or artificial extracorporeal perfusion technology. Viability of the isolated cerebral organ was primarily determined by the quality of the electroencephalographic activity (EEG.)

While all the solid organs had been surgically isolated and maintained on appropriate mechanical circulatory systems by the 1950s, this had not been accomplished with the brain. Many attempts had been undertaken and had failed, which led to the belief that to create an isolated brain model was impossible. However, the solution to the problem was finally solved in 1962. It was demonstrated, for the first time, that the most complex tissue in the biological universe could be successfully sustained by artificial perfusion systems.

This discussion will provide a brief history of the development of the isolated brain model stressing how the anatomical, surgical and rheological difficulties were finally overcome. The availability of this unusual cerebral preparation now offered the investigator unique opportunities to study brain performance that would be impossible to undertake in an intact cerebral system. The results of experiments utilizing this special brain preparation emphasizing its normality of function, its performance under extreme conditions of deep hypothermia (15° C), and circulatory arrest will be presented. The impact of these discoveries on human cerebral function will be examined.

A TRIPTYCH OF THE READING BRAIN:
EVOLUTION, DEVELOPMENT, PATHOLOGY AND ITS INTERVENTION

MARYANNE WOLF

Pascal once wrote that there are few new thoughts on the earth, but there *is* rearrangement. Similarly, there are no new structures in the brain's recent evolution, but there is an extraordinary potential for rearrangement of its existing circuitry. Underlying the acquisition of each new skill learned by our species lies a capacity to rearrange and forge whole new connections and pathways among structures originally designed for other things: the ability to see a visual pattern, to retrieve a word for a predator, to infer that a footprint augurs danger. The human brain's remarkable capacity to make novel connections within itself is the neurological basis for most of our species' cognitive leaps and inventions.

Nowhere is this more in evidence than in the history of written language, in its development in the child, and in the reasons for its breakdown. Reading or written language represents one of the major breakthroughs in the cognitive evolution of the species. Both its physiological structure and its development reflect and re-enact the brain's intrinsic capacity for rearrangement and for learning to use what is genetically given to go beyond it. The study of reading development and the factors that derail it (pathology) offers cognitive neuroscientists a superb example of how the brain learns a recently acquired cognitive skill through the rearrangement of older neurological structures.

This paper will describe a research program that uses evidence from reading evolution, development, and pathology to construct a broadened conceptualization of both reading and reading breakdown in developmental dyslexia. Within this conceptualization dual emphases will be placed on the heterogeneity of different subtypes in dyslexia and the concomitant need for more comprehensive approaches to reading intervention for children with dyslexia.

Towards those ends, a new form of reading intervention will be described that is based on an evolving model of the reading brain, on an understanding of dyslexia subtypes, and on 'best practice' in educational research. Preliminary data from a five-year comparative study of this new program with other well-documented approaches to reading intervention will be presented. These results will be placed within the context of how an understanding of reading's evolution, development, and pathology informs treatment and, at the same time, contributes to our understanding of how the brain learns.

* * *

Working Group on:

STEM CELL TECHNOLOGY AND OTHER INNOVATIVE THERAPIES

Significant advances in our knowledge of the early development of the mammalian embryo were made when fertilization of the mammalian ovocyte became possible in vitro. The development of the egg could then be directly studied up to the blastocyte stage. Moreover, in 1981, it was shown that the inner cells of the mouse blastocytes could be maintained in culture in a multipotent and proliferative state. From then on, lines of embryonic stem cells were derived from embryos and cultured for long periods of time. A transient stage of normal development could thus be 'captured' in vitro by culturing the early cells of the blastocyst in appropriate conditions. Even more important is the fact that these multipotent cells can be induced to differentiate into various cellular phenotypes if they are subjected to definite sets of growth and differentiation factors. These results suggested that embryonic stem cells (ES cells) could be used for therapeutic purposes in various diseases. Experiments currently carried out in mice confirm this prospect.

In 1998, ES cells were derived from human embryos by a research group in the United States. Several human ES cell lines are now established and the possibility that they are used for cellular therapies in humans is being discussed. However, utilisation of human embryos for such purposes raises ethical issues that have to be carefully considered before these techniques are developed.

Another advance that came from the work of Cell and Developmental Biologists concerns stem cells present in most tissues and organs of the adult body. These cells are endowed with potentialities that are broader than previously thought and may become a source of cells for replacement therapies.

In the Symposium organized on November 10-11, 2003 at the Pontifical Academy of Sciences, an account of the state of the art in the field of stem cell biology will be given by the leading experts in the field. Their possible use in human therapy on the basis of experiments that are carried out on the mouse model will be particularly discussed.

Prof. N. Le Douarin, from the Collège de France (Paris), will introduce the subject.

Prof. I. Weissmann, from Stanford University (USA), who has a longstanding experience in the field of hemopoietic and other kinds of stem cells will provide the attendants with an overview of the stem cell field and Prof. Ron McKay will compare the properties of stem cells from diverse sources: embryonic, foetal and adult. Certain cells remain undifferentiated during embryonic development and become, in the adult, the source of the gametes. They constitute a permanent link between generations. Germ cells possess characteristics that are also found in stem cells. This important subject will be discussed by Prof. Azim Surani from Cambridge (UK).

The actual potentialities of adult stem cells will be reviewed by Prof. Helen Blau from Stanford University and Prof. Rudolf Jaenisch from the MIT (Cambridge, USA) will give a survey on possible applications of the nuclear transfer technique. The data provided by the experts will be the subject of a general discussion chaired by Prof. Ann McLaren, one of the top international specialists in the field of mammalian development. Prof. McLaren is in charge of high responsibilities in the field of ethics in the United Kingdom.

Remarkable progress in the knowledge of the human genome is leading to new therapies based on a precise understanding of the gene alterations that cause the diseases and the characteristics of the diseased cells. Assessment of the genes expressed by patients both in their normal and diseased cells will lead to treatments that will be more efficient at correcting the defect of diseased cells or at eliminating these cells, while being better tolerated by the patient.

In the field of cancer treatment, important new approaches are based on very specific inhibitors of precisely defined over-active gene products. Another therapeutic modality that benefits from a precise knowledge of the genes abnormally activated in cancer cells is immunotherapy. Cancer cells bear antigens that are not present in the normal cells of the human body, because the genes that code for these antigens are only active in cancer cells. These antigens are recognized by T lymphocytes. A large number of clinical studies aimed at vaccinating cancer patients with tumor-specific antigens, are presently ongoing. Significant tumor regressions are observed in about 10% of the patients, in the absence of any significant toxicity. The factors that limit the efficacy of these treatments are under intense study.

Another area to be discussed will be gene therapy targeting hematopoietic stem cell defects. Severe combined immunodeficiency will be taken as a model. Evidence will be presented that retroviral mediated gene transfer can target stem cells and provide sustained development of a functional immune system. The risks and consequences of an adverse effect caused by insertional mutagenesis will be described and discussed. How to improve and extend the usage of this strategy will be presented.

* * *

ABSTRACTS

REPAIR OF ADULT TISSUES BY ADULT BONE-MARROW-DERIVED STEM CELLS

HELEN BLAU

Our laboratory has long been interested in the regulation of cell differentiation. Years ago we showed in cultured cells that the differentiated state of adult human cells is reversible and can be reprogrammed, contrary to prevailing dogma. The expression of human muscle gene products was induced following fusion of mouse muscle cells with diverse cultured human adult cells in stable non-dividing heterokaryons. These unexpected findings showed that the differentiated state was plastic and could be changed. Recently, work in our laboratory has focused on the exciting finding that cells in adult bone marrow (stem cells) are reprogrammed naturally in adult mice and humans. After a bone marrow transplant, genetically marked marrow-derived cells contribute to certain muscle and brain cells. Indeed, a single hematopoietic-stem-cell yields both blood and muscle, a clear demonstration of plasticity *in vivo*. We have shown that reprogramming, or changes in nuclear gene expression, can occur by two different mechanisms. In muscle, marrow-derived cells are reprogrammed and undergo a cell fate change in response to the extracellular microenvironment, or niche. In brain, marrow-derived cells are reprogrammed as *in vivo* heterokaryons that form by fusion with Purkinje neurons and activate Purkinje genes in response to intracellular signals. Such stable binucleate non-dividing fusion products increase in number and persist for most of the life of the mouse, suggesting a fusion-based repair mechanism for complex cells that cannot be made anew in adulthood. Neither a bone marrow transplant nor the irradiation that accompanies a bone marrow transplant are prerequisites for the observed changes in cell fate. However, local damage and the signals resulting from tissue injury are necessary and sufficient. We propose that hematopoietic stem cells constitute a previously unrecognized tissue repair pathway with access to the entire body via the blood.

* * *

THIERRY BOON-FALLEUR

Cancer cells bear antigens that are not present on the normal cells of the human body. These antigens are recognized by T lymphocytes, which are, in principle, capable of destroying the cancer cells, even though they clearly fail to do so in most instances. A large number of clinical studies aimed at vaccinating cancer patients with tumor-specific antigens, are presently ongoing. Significant tumor regressions are observed in about 10% of the patients. The factors that limit the efficacy of these treatments are under intense study.

* * *

ALAIN FISCHER

My talk will address the feasibility of gene therapy targeting hematopoietic stem cells. Severe combined immunodeficiency – a favorable setting – will be taken as a model. Evidence will be presented that retroviral mediated gene transfer can target stem cells and provide sustained development of a functional immune system. The risk and consequences of an adverse effect caused by insertional mutagenesis will be described and discussed. This leads to an assessment of the benefit/risk balance. How to improve and extend the usage of this strategy will be presented.

* * *

THE BIOLOGY OF NUCLEAR CLONING AND THE POTENTIAL
OF EMBRYONIC STEM CELLS FOR TRANSPLANTATION THERAPY

RUDOLF JAENISCH

An emerging consensus is that somatic cell nuclear transfer (SCNT) for the purpose of creating a child (also called 'reproductive cloning') is not acceptable for both moral and scientific reasons. In contrast, SCNT with the goal of generating an embryonic stem cell line ('therapeutic cloning') remains a controversial issue. Although therapeutic cloning holds the promise of yielding new ways of treating a number of degenerative diseases, it is not acceptable to many because the derivation of an embryonic stem cell line from the cloned embryo (an essential step in this process) necessarily involves the loss of an embryo and hence the destruction of potential human life.

In my talk I will develop two main arguments that are based on the available scientific evidence. 1) In contrast to an embryo derived by *in vitro* fertilization (IVF), a cloned embryo has little if any potential to ever develop into a normal human being. This is because, by circumventing the normal processes of gametogenesis and fertilization, nuclear cloning prevents the proper reprogramming of the clone's genome, which is a prerequisite for development of an embryo to a normal individual. It is unlikely that these biological barriers to normal development can be solved in the foreseeable future. Therefore, from a biologist's point of view, the cloned human embryo, used for the derivation of an embryonic stem cell and the subsequent therapy of a needy patient, has *little if any potential* to create a normal human life. 2) Embryonic stem cells developed from a cloned embryo are functionally indistinguishable from those that have been generated from embryos derived by *in vitro* fertilization (IVF). Both types of embryonic stem cells have an *identical potential* to serve as a source for therapeutically useful cells.

It is crucial that the ongoing debate on the possible therapeutic application of SNCT is based on biological facts. Taking into consideration the body of research from animal experiments should provide a basis for a more rational discussion that is founded on scientific evidence rather than on misconception or misrepresentation.

* * *

CONTROLLING THE DIFFERENTIATION OF HUMAN ES CELLS

RONALD MCKAY

Work from our group played an important role in the early period when stem cells of the central nervous system were first defined and we are now focused on understanding three linked major processes in the developing nervous system: (a) cell cycle control (Tsai, R. Y. and R. McKay *Genes & Dev.* 16:2991-3003, 2002), (b) the choice of cell fate (Panchision, D. M. et al. *Genes Dev.* 15: 2094-2110, 2001) and (c) the differentiation of stem cells to electrophysiologically functional neurons (Vicario-Abejon, C. et al. *Eur.J.Neurosci.* 12: 677-688, 2000). New advances in stem cell biology might help us understand how different components or modules of development cooperate to generate functional tissues. Work from our lab shows that embryonic stem cells can be efficiently guided to neuronal and glial fates that integrate into the neo-natal and adult brain (Studer, L. et al. *Nat.Neurosci.* 1: 290-295, 1998; Brustle, O. et al. *Science* 285: 754-756, 1999; Lee, S-H. et al. *Nat.Biotechnol.* 18: 675-679, 2000; Kim, J-H. et al. *Nature* 418: 50-6, 2002.). Similar strategies generated endodermal fates from ES cells (Lumelsky, N. et al. *Science* 292: 1389-1394, 2001). The lack of control of differentiation limits interest in human ES cells. We have now shown that external signals can control the generation of neuronal precursors, non-neural germ layer-specific precursors, extra-embryonic endoderm and primitive germ cells. Electrophysiologically, synaptically active neurons and differentiated endodermal cells can be efficiently derived, confirming the developmental potency of these precursors. These data suggest that controlled access to many cell types and the developmental decisions that generate them can be achieved. Routine access to functional cells generated by controlled in vitro differentiation has implications for embryology and reinforces the wide range of clinical uses for ES cells.

* * *

FRANÇOIS SIGAUX

Considerable achievements have been obtained during the past few years in research against cancer. The subtle alterations necessary to the neoplastic transformation of a normal cell are now known. Deregulating cell cycle, apoptosis and senescence, genetic and epigenetic acquired events allow a darwinian process to select rare cells for immortalization. Frequent genomic instability increases the probability to accumulate other events allowing the targeted cells to stimulate angiogenesis, migrate in the body and develop metastases in distant sites. Although the repertoire of these functional alterations is quite invariant from a type of cancer to another one, the relevant catalogue of genetic and epigenetic events vary defining a molecular signature that is characteristic of a given tumor in a given patient. Defining these tumor identity cards represented up to now a formidable task. Major progresses in genome sequencing and in large scale genomics allow now to establish near complete catalogues in many patients and for a large number of tumor types. These molecular portraits represent an opportunity to define personalized medical tools and to design new drugs or therapies based on critical genes defined by multidimensional statistical analyses of experimental data correlated with patient and gene annotations. Although major successes were recently obtained in this field, the processivity of this strategy remains low, essentially due to the only partial knowledge of gene networks in normal and neoplastic cells. Defining these networks is also essential in order to design multi-therapies targeting independent pathways. Extracting sense from the genome and reducing complexity to model cancer cells is therefore a limiting step which requires extensive cooperations between cell biologists and mathematicians and is the new challenge of the current research against cancer.

GERM CELLS: THE ETERNAL LINK BETWEEN GENERATIONS

AZIM SURANI

The fertilised egg lives indefinitely, inasmuch as it gives rise not only to a new individual, but theoretically at least, to an endless series of generations. Thus the oocyte is potentially totipotent. However mammals are unique amongst vertebrates since the genetically identical sperm and oocyte are functionally non-equivalent. This is because of genomic imprinting during gamete formation so that expression of certain genes is strictly according to their parental origin. For this reason, parthenogenetic development is not possible in mammals since both the functionally non-equivalent sperm and oocytes are needed to generate a new individual.

The establishment of the germ cell lineage itself is amongst the first to occur during development. In many organisms, this decision is implemented according to the preformistic model through the inheritance of preformed germ plasm in cells destined to form germ cells. By contrast, in mammals, germ cell specification occurs according to stem cell model that first requires development of the pluripotent epiblast cells. In mammals, such cells develop by the blastocyst stage. Some maternally inherited molecules present in the oocyte may have a critical role in generating this pluripotent epiblast. These epiblast cells then respond to signalling molecules, which lead to the specification of germ cells and soma. Germ cells subsequently undergo extensive genomic reprogramming to erase and re-initiate a new cycle of genomic imprints. The mechanisms and molecules involved in this process may partly correspond to the mechanisms required to convert a somatic differentiated cell into a pluripotent cell. Furthermore, it is also possible to generate pluripotent stem cells directly from mouse and human germ cells. These pluripotent stem cells are quite similar to embryonic stem cells generated from epiblast cells. This is an example of how a highly specialised cell may undergo dedifferentiation to pluripotency.

* * *

STANDING RULES FOR MEETINGS

1. The Academy invites a number of illustrious scholars who have especially studied a given question and have arrived at different conclusions to meet in Rome at its headquarters, the 'Casina di Pio IV', situated in the Vatican City, so as to make a joint examination of all the data on the question.

2. The chief aim of these discussions is to endeavour to reach a common view on the subject of the meeting, but when this is not possible to formulate precisely the reasons for this inability. The scholars invited to these meetings undertake in advance to concentrate their efforts on this.

3. A critical examination of these reasons should lead either to agreement on a partial or provisional solution or else to the conclusion that, on the basis of the information presently available, it is impossible to establish unity on the question concerned. In the latter event the scholars involved will be called upon:

- a) to define the reasons why agreement appears to be impossible for the present;
- b) to specify the kind of research work it would be desirable to undertake in order to solve the problem.

4. The invitation will be addressed by the Academy to only a small number of representatives of each branch of learning: these will be selected from scholars who are not connected with the Academy. These representatives will be joined during the discussions by members of the Academy who are experts in the same discipline. This invitation, moreover, will apply only to the study of one precise question by each branch of learning.

5. The debates will be strictly private and will take the form of papers and talks in the presence only of a few members of the Pontifical Academy of Sciences who have special knowledge of the subject under discussion. Interpreters will be made available to the participants.

6. The conclusions arrived at will be published in the form of a 'Statement' (to which may be added individual notes) mentioning:

- a) the points on which agreement was reached;
- b) the points on which it was impossible to reach agreement;
- c) the reasons why it was not possible to reach agreement;
- d) suggestions about the research work that appears most appropriate in order to arrive at a solution of the difficulties.

7. The 'Statement' arrived at will be immediately printed and transmitted by the Pontifical Academy of Sciences to all the centres of learning which might be interested in it.

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MEMORANDUM

Every day a bus will leave the hotel (8:45) for the Academy fifteen minutes before the beginning of the morning session (9:00). At the end of the morning session a bus will take the participants to the Domus Sanctae Marthae for lunch. After lunch it will take them from the hotel to the Academy for the afternoon session (14:45). A bus will also depart from the Academy following each afternoon session (about 19:00) to take participants back to the hotel.

For the participants lodged at the Residenza Paolo VI and the Residenza Palazzo Cesi, lunches and dinners will be offered at the Domus Sanctae Marthae from 7 to 11 November 2003. However, please confirm your presence with the Secretariat.

Saturday 8 November a private guided visit to the Vatican Museums (Museo Pio Clementino, Apollo, Laocoon, Belvedere Torso) has been organized for the participants at the end of the afternoon session (about 19:00).

Sunday 9 November (9:30), Holy Mass will be celebrated by His Eminence Cardinal Carlo Maria Martini at the Church of St. Stephen of the Abyssinians; afterwards a morning session will be held at the Casina Pio IV. Lunch will be served at the headquarters of the Academy; then a private guided visit to the Sistine Chapel has also been organised for the participants (15:30).

The cost of travel will be covered by the Pontifical Academy of Sciences. If you purchase your travel ticket yourself (which is normally the best policy), you will be refunded for a sum equivalent to the economy class fare.

Note: Please give your form for the refunding of expenses to the secretariat of the Academy at least one day before your departure so that you can be refunded immediately.

The PONTIFICAL ACADEMY of SCIENCES

Working Group on
MIND, BRAIN, AND EDUCATION

**THE SESSION COMMEMORATING THE 400TH ANNIVERSARY
OF THE FOUNDATION OF THE PONTIFICAL ACADEMY OF SCIENCES (1603-2003)**

Working Group on
STEM CELL TECHNOLOGY AND OTHER INNOVATIVE THERAPIES

Casina Pio IV, Vatican Gardens
7-11 November 2003

