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EDITORIAL

Stem cell research: Biology's new frontier

'All cells come from cells'.
– *Rudolf Virchow*

The provocative title of a recently published paper, 'Turning Blood into Brain' (Mezey, E. *et al*., *Science*, 2000, **290**, 1779) draws attention, forcefully, to biology's latest battleground – stem cell research. The same issue of the journal carries another report, more circumspectly titled, 'From Marrow to Brain (Brazelton, T. R. *et al*., *Science*, 2000, **290**, 1775). What these reports, and many others appearing in the current scientific literature, promise is a 'brave new world' of biomedicine, where stem cells may provide the basis for treatment of many types of tissue and organ damage. The possibilities that appear on the anvil are the 'use of cardiac muscle cells for heart problems, liver cells for hepatitis, and neural cells for Parkinson's and Alzheimer's disease' (McLaren, A., *Science*, 2000, **288**, 1775). Cell biology has reached its present state after over one and a half centuries of progress, since Theodor Schwann first propounded the cell theory of biology in 1839. Schwann brought reductionism to biology; complex organisms could be viewed as a collection of cells, whose properties determine an organism's future. The years after Schwann were to take reductionism further; biochemistry, which reduces cells to a complex collection of interacting molecules was born at the end of the 19th century, midwifed into existence by Buchner's experiments on extracts of yeast. The tide of 'ultimate reductionism' that swept 20th century physics and chemistry, a belief that atoms, protons, electrons, quarks and a host of others (and even more recently, 'superstrings'), will provide a complete understanding of matter, presumably both inanimate and animate, left its imprint on biochemistry. The gulf between cell biology and biochemistry has really defined the difference between the living and the non-living. Single-cell organisms, bacteria pre-eminent among them, replicate with astounding fidelity and multiply rapidly; reproduction is indeed, the most remarkable attribute of life. Despite the power of modern chemistry and biochemistry, the ability to create 'synthetic life' is confined to the scientists featured in comic strips and science fiction.

But, cells and their aggregates can be manipulated. Over a century ago, Hans Driesch showed in a classic set of experiments that each cell of a two or four cell sea urchin embryo developed separately 'into perfectly formed embryos'. Clearly, individual embryonic cells possess a genetic program for development, which is an intrinsic property of the cell. Today's excitement about stem cell research and animal (and possibly, human) cloning experiments derives from the remarkable ability of some cells to multiply and differentiate under appropriate conditions. The pace of research in cell biology, in the three years since the arrival of the world's first 'cloned sheep', Dolly, has been dramatic. The production of ANDi (inserted DNA spelled backward; black humour evident even in the christening), the first genetically engineered rhesus monkey, marks the beginning of a new era, where mammals, even man, may be produced in genetically modified form. The arguments for creating genetically modified ('transgenic') monkeys appear impeccable; after all, primate models for many human diseases do not exist. The hope is that future medical advances will undoubtedly be made on the basis of research with genetically engineered monkeys.

But, we must return to stem cells. The cell biology texts list the 'defining properties' of these cells: (i) They are not 'terminally differentiated'; in simpler terms, the cell's ultimate fate has not been defined as yet, leaving open the possibility that stem cell differentiation can be controlled. (ii) Stem cells may divide without limit (an added caveat, in the 'Molecular Biology of the Cell' by Alberts *et al.* states 'or at least for the lifetime of the animal.'). (iii) When stem cells divide, the daughters appear to have a choice; they can either continue as stem cells, eternally youthful, untouched by the transition to adulthood. Alternatively, they can embark on a course that leads to terminal differentiation, sealing their fates for example, as liver, kidney or brain cells.

Nature appears to have endowed stem cells with many of the properties that we all seek, eternal youth and a whiff of immortality. Stem cells are found quite widely, particularly in tissues with a rapid turnover; the most widely known example being the bone marrow, from where the diverse cells of the blood are derived by differentiation. The recent papers of Mazey *et al.* and Brazelton *et al.* in *Science* demonstrate that adult bone marrow cells when transferred into mice, appear to find their way to the brain (a not entirely surprising finding) and express the characteristic features of neurons (a remarkable discovery). Translating these findings into practical therapeutic advances will undoubtedly be a formidable task, but the prospects are immense.

This elementary and clearly oversimplified consideration of recent advances in cell biology would be out of place in an editorial column, but for one fact; embryos and fetuses are a rich source of undifferentiated cells, with the spectacular ability to differentiate and integrate into tissues. For human therapies, which may determine future treatment of diseases from Parkinson's and Alzheimer's to diabetes, we must, necessarily, turn to human stem cells. How much research can be carried out on human embryos? The questions regarding human stem cell research, using embryonic cells, are complicated by the fact that the technologies closely border those that may be used in human reproductive cloning. The ethical questions involved must be addressed, eventually, by governments, legislatures and regulatory bodies. Countries like Japan, Germany, Sweden, UK, Australia, the European Union and the United States have already embarked on a detailed consideration of the issues involved (*Science*, 2000, **290**, 1673). In all cases, legislative guidelines on the permissible limits of research in the area are likely to be spelled out. The House of Commons in Britain has just passed amendments to the Human Fertilization and Embryology Act, 1990, to allow the use of human embryos for research. The opponents of these changes argue that the British legislators have taken the first steps down the 'slippery slope towards human cloning'. (Dickson, D., *Nature*, 2001, **409**, 5). The Europeans and others appear to be more conservative, with the European Group on Ethics in Science and New Technologies suggesting, that 'at present the creation of embryos for somatic cell transfer would be premature' (*Nature*, 2000, **408**, 277). But, the proponents of stem cell research argue that distinctions must be made between (i) embryos donated for research by patients undergoing *in vitro* fertilization treatment ('spare embryos'); (2) embryos made for research by fertilizing donated oocytes *in vitro* ('research embryos') and (3) embryos made for research by transfer of somatic nuclei to donated oocytes ('nuclear transfer embryos') (McLaren, A., *Nature*, 2000, **408**, 573). At present the use of human 'research embryos' and 'nuclear transfer embryos' are considered ethically unacceptable, while work with 'spare embryos' appears to cause less discomfort. Biology's advances have posed new ethical dilemmas for which no easy answers appear to be forthcoming.

But, what of Indian research? There is little by way of organized stem cell research that is visible as yet. However, it would not come as a surprise if stem cell research is soon hailed as the new frontier in biotechnology and biomedical research, by our government agencies. When that happens we may have to address ethical issues with a degree of understanding and patience that is not easily found. Our legislators find it hard even to discuss the annual budget in a constructive fashion; complex ethical issues may scarcely merit any attention. Unfortunately, committees of scientists are often no better. The attitude that 'we know best', which has pervaded governmental decision making, almost exclusively dominated by directly interested departments, in areas as diverse as atomic energy and genetically modified crops, does not augur well for an informed debate on the complex issues, which must eventually be faced in the area of human stem cell research.

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