Hematology has played a major role in the research area of somatic stem cells since the XX century. In 1868, Bizzozzero and Neumann independently found nucleated blood cells in the bone marrow squeezed from the bone tissues of human cadavers\cite{1,2}. The authors suggested that marrow was the major source of blood cells and, in Germany, these cells were called “Neumann zelle”\cite{1,3}. Interestingly, Bizzozzero also claimed that future studies of bone marrow patients would improve and clarify our understanding of leukemia\cite{4}.

In 1917, Pappenheim and Ferrata demonstrated the existence of an undifferentiated stem cell in human bone marrow which, after an intermediate state of transit cells gave rise mature blood cells\cite{5,6}. Pappenheim called this primordial cell “gemeinsame stamzelle” and Ferrata “emoistioblasto”, the “Ferrata cell” in Williams and Beutler’s book Hematology (1972). Pappenheim founded “Folia Haematologica” and Ferrata “Haematologica”, which is still being published.

In 1945, the devastating use of nuclear weapons in Hiroshima and Nagasaki stimulated Lorenz and Jacobson to investigate the efficacy of bone marrow injections in irradiated mice, and reported increased survival in the treated animals\cite{9,10}. On the basis of these results, six physicists accidentally exposed to enormous amounts of gamma and neuron irradiations were given multiple bone marrow infusions, and four of the six survived\cite{11}.

In the second half of the last century, another area of research investigated cell differentiation during embryogenesis in animals and humans, and it was found that, when transplanted, isolated embryonic stem cells were capable of differentiating into various tissues and that their capacity of differentiation could be renewed by cloning mammal embryonic cells from the nucleus of adult tissue\cite{12-15}.

The increasing number of bone marrow transplants in humans (mainly in cases of hematological malignancies and cancer) led to improvements in experimental and clinical stem cell research, and it was found that HSCs could be engrafted in various tissues of transp-
lanted animals and humans, where they differentiated into mature organ cells. The list of tissues using the blood model of differentiation from stem cells to transit cells to mature cells includes skeletal muscle, epithelium, intestine, liver and the nervous system\cite{16-25}. It was also shown that stem cells repopulate injured tissues in experimental animals\cite{26,27}.

Somatic stem cells (outside adult bone marrow) were firstly discovered in peripheral blood and later on in the central nervous system and skeletal muscle during the last decade of the XX century\cite{28,29}. The potential of adult somatic stem cells to differentiate into cells other than those from which they were generated (be they in the same or different germ layers) has recently been demonstrated, and it has been found that, when transplanted in some patients, peripheral blood HSCs differentiate into mature hepatocytes as well as epithelial cells of the skin and gastrointestinal tract\cite{30-34}.

However, these studies gave rise to some basic questions concerning the role of the microenvironment in stem cell de-transdifferentiation and the presence of stem cell contaminants in transplanted bone marrow\cite{35,36}.

Evidence of de-transdifferentiation from HSCs to other tissues was provided by means of single transplantations of HSCs that differentiated in the tissues of mice and fetal sheep, and the fact that the transplantation of clonally derived multipotent adult progenitor cells (MAPC) into P1-P3 rats led to the formation of hematopoietic stem cells, astrocytes, oligodendrocytes and neurons\cite{37-39}. The demonstration of stem cell plasticity and the development of therapeutic approaches involving the transplantation of stem cells into the diseased tissues of experimental animals has captured the imagination of clinicians, stimulated interest in clinical trials, and raised the hopes of patients.

It was found that whole bone marrow transplantations in some patients with osteogenesis imperfecta increased bone density and growth rates partially because of the contribution of donor osteoblasts\cite{40}.

Therapeutic bone marrow transplants led to the development of hepatocytes and cholangiocytes from donor stem cells in six human recipients and, when neurons differentiated in vitro from human precursor cell lines were implanted in the central nervous system of 12 stroke patients, some of them showed albeit incon-
sistent signs of improvement\cite{41,42}.

The transplantation of stem cells into the central nervous system of humans suffering from neurodegenerative diseases was tested in several trials during the 1990’s. It is estimated that, partially because of general population aging, more than 25 million people in the Western World will have neurodegenerative diseases in the next few decades. Little is known about the etiopathogenesis of many of these diseases, such as Parkinson’s (PD) and Alzheimer’s disease (AD), and the same is true in terms of their prevention and treatment. Depending on the drug used (L-dopa, dopamine agonists, anticholinergic agents or selective monoaminooxidase B inhibitors) the treatment of PD patients can have significant side effects that are sometimes so severe as to make it totally impossible for them to move (OFF). Neurosurgical treatment has become increasingly important since the development of techniques for the deep stimulation of subthalamic nucleus (DBS) in the 1990s, but seems to be reserved for patients who no longer respond to drug therapy in severe clinical condition. Physical and logotherapy are useful aids, but not resolutive.

The results of cerebral neuroimplantology in PD patients have opened up new therapeutic perspectives for neurodegenerative diseases, and more than 300 patients throughout the world have so far been implanted\cite{43,44}. The transplantations were performed by injecting tissue fragments of aborted human embryos. Almost all of the reports describe moderate motor symptom improvements in patient subgroups but both European and American studies found that the patients experienced troubling side effects after transplantation. For both practical and biological reasons, it seems unlikely that the transplantation of fetal tissue fragments will become the therapy of the future because intratissue heterogeneity is a major barrier to reproducibility and the number of fetuses required to treat even a few patients is a serious limitation.

It has been suggested that the use of immortalised cell lines derived from human embryo or fetal stem cells may be a more reliable therapeutic approach as such cells have already been successfully transplanted in animal models of neurodegenerative diseases (PD, motoneuron disease and spinal cord injury). However, the use of cell lines derived from pluripotent embryonic or fetal stem cells raises a number of questions: The injection of totipotent embryonic cells into mature mice
has sometimes caused teratoma; it is still difficult to inject cells that are not recognised as foreign by the recipient immune system (as in the case of autologous transplantation); and, finally, the use of such cell lines is fraught with profound ethical issues[45].

The demonstrated plasticity of stem cells from alternative sources, such as hematopoietic bone marrow or cord blood, offers a possibly more practical means for clinical trials in patients with neurodegenerative diseases[46,47]. The forthcoming medical challenges include the expansion of isolated allogeneic or autologous stem cells, appropriate in vitro neuroglial orientation by means of epigenetic conditioning, and their careful validation in animal models of PD[48].

REFERENCES


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