Guest Article

Reproductive Technology and Regenerative Medicine

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Ageing of the population is one of the most important developments of the 20th century and will be one of the challenges of the near future. National and international efforts to reduce child and maternal mortality and to lower the incidence of infectious and parasitic diseases, together with improvements in nutrition, education, income and health services, have led to a considerably longer life span. This combination of longer life and sustained reductions in fertility throughout previous century has created increasingly larger numbers and proportions of elderly. In developed countries, ageing is already creating many problems and challenges for policy makers. Ageing will also hit developing countries in the near future. Proportions of elderly are still relatively low in developing countries and ageing is not yet considered an urgent issue. However, fertility declines are expected to occur over a much shorter time span than in developed countries. Because developing countries have fewer financial resources, policy options in response to ageing will require careful planning. Social security schemes currently used by developed countries will be unaffordable in most developing countries. Absolute number of elderly in the world will grow from 385 million at present to 1.5 billion in 2050 (World population projections 1998). In many developed countries, the number of elderly persons will increase considerably around 2030 as the baby boom children of the 1960s enter the oldest population cohorts.

Ageing will accelerate between 2025 and 2050. In that period, only the oldest age cohorts (70-74, 75-79 and 80+) will grow by more than 50% (U.N. Population Ref. Bureau 2001). As life expectancies increase, growing proportions of the population will survive the age of 80 years. In many countries, the oldest old are the fastest growing part of the elderly population. In 1997, the oldest old represented only 1.1% of the world population (0.6% in developing countries and 3% in developed countries) (United Nation 2001). As a result, the number of oldest old will explode : in 2050 the number of oldest old will be more than six times as high as in the beginning of present century (423 million vs. 70 million).

Within the next 25 years, mean life expectancy at birth will increase. The fastest progress is anticipated in countries with low life expectancies at present. Since the 1950s, the increase in life expectancy at birth has shown marked differences between males and females. While female life expectancy continued to rise in most developed countries, gains in male life expectancy slowed down or stabilized. In developing countries, female advantage is usually lower than 5 years. In developing countries, the majority of all deaths (17 million out of 40 million) were due to infectious and parasitic diseases in 1996. On the other hand, in developed countries, circulatory diseases (heart disease, stroke, hypertensive disease) are the main causes of death (5 million out of 12 million deaths) (World Bank, 1998).

The consequence of the demographic transition and the shift to the lower fertility and mortality has been the evolution in the age structure of the world population. The declining population under age 15 and increasing population aged 65 and above, are likely to have wide-ranging economic and social consequences. This inter-generational transfers will have impact on economic growth, savings and investments, labour markets, pension schemes, health services and long term care, family structure and living arrangements, socio-economic status of older persons, also on productive ageing and quality of life.

Women Aging

Women outlive men in virtually all societies; consequently in very old age, the ratio of women/men is 2:1. Yet while women generally live longer than men, for

many of them greater life expectancy carries no real advantage in terms of additional years lived free of disability. Women's health is influenced by their status in society. In many parts of the world, discrimination against women begins before they are born and stays with them until they die. The status of women's health in old age is shaped throughout their lives by factors over which they have little if they control. Many millions of women are made old before their time by the daily harshness and inequalities of their earlier lives, beginning in childhood. They experience poor nutrition, reproductive ill health, dangerous working conditions, violence and lifestyle related diseases, all of which exacerbate the likelihood of breast and cervical cancers, osteoporosis and other chronic conditions after menopause

Aging and Chronic Disabilities

The increased life expectancy in recent years and in the future decades, together with changes in lifestyle stemming from socioeconomic development, will be linked with increase of circulatory disorders, cancer, and some forms of mental illness. Coronary heart disease and stroke account for 12 million deaths a year cancer 6 million, and 3 million deaths are due to chronic obstructive pulmonary disease (WHO,2002). There is a steady increase of patients suffering of cancer. In several newly industrialized regions cancer has become, unexpectedly quickly, one of the leading causes of death. Cancer of the breast, colon and prostate have emerged in several countries in which they were hardly known in past. For all countries, breast cancer is the most common in women, followed in affluent countries by colorectal, lung and stomach cancers. In developing areas, cervical cancer is second, followed by stomach cancer. In men more cases of prostate cancer are diagnosed. Population ageing is the main factor responsible for the high incidence in diabetes mellitus and its complications. Along with increased longevity and socioeconomic development has come an increase in some forms of mental disorders and environmental and occupational hazards.

Human aging is characterized by progressive constriction of the homeostatic reserve of every organ system. This decline is gradual and progressive, although the rate and extent of decline vary. The decline of each organ system appears to occur independently of changes in other organ systems and is influenced by diet, environment, and personal habits as well as by genetic factors. An abrupt decline in any system or function is always due to disease and not to normal aging. Normal aging can be attenuated by modification of risk factors. In the absence of disease, the decline in homeostatic reserve causes no symptoms and imposes few restrictions on activities of daily living regardless of age. Much can be done to prevent the progression and even the onset in older people.

The clinical applications of human embryonic stem cell (ES), therapeutic cloning opens new horizon in medicine and especially for aging patients.

Embryonic Stem Cells

Stem cells - cells that have the ability to divide for indefinite periods in culture and to give rise to specialized cells. In the very early stages of embryonic development, cells have the capability of dividing indefinitely and then differentiating into any type of cell in the body. Recent studies have revealed that much of this remarkable developmental potential of embryonic stem cells is retained by small populations of cells within most tissues in the adult. The development of stem cell lines that may produce many tissues of the human body is an important scientific breakthrough. Transplanted stem cells will allow them to replace lost or dysfunctional cell populations in degenerative disorders. This research has the potential to revolutionize the practice of medicine and improve the quality and length of life. At present, human stem cell lines have been developed from two sources with methods previously developed in work with animal models.

a. Human embryos 5- to 9 - week post fertilization, obtained as a result of therapeutic termination of pregnancy. The cells were obtained from gonadal ridges and mesenteries of human embryos (Shamblott et al 1998).
b. Stem cells were isolated directly from the inner cell mass of human embryos at the blastocyst stage, received from IVF clinics. These embryos were in excess of the clinical need for infertility treatment and embryos were made for purposes of reproduction (Thomson et al 1998).
c. Trials have been carried out to obtain human stem cells by somatic cell nuclear transfer (SCNT), a method successful in animal models.

There are several important indications why human stem cells lines formation is important to advances in health care. Research on stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the identification of the factors involved in the cellular decision-making process that results in cell specialization. For this it is need to grow stem cells on a large scale, to introduce genetic modifications into them and to direct their differentiation. To guide different stem

cells into the desired lineage requires the identification of factors that direct their differentiation. There are several potential applications of stem cell technology in human medicine: basic embryological research, functional genomics, growth factor and drug discovery, toxicology and cell transplantation. Some of serious medical conditions, such as cancer and birth defects, are due to abnormal cell specialization and cell division.

Most important clinical pathological conditions result from disruption of cellular function or destruction of tissues of the body. Stem cells, stimulated to develop into specialized cells, offer the possibility of a renewable source of replacement cells and tissue to treat diseases, conditions, and disabilities, common in aging patients.

Neurological Disorders

Demyelination is the major pathology in diseases of nervous system. Animal experiments, showed that transplanted myelinogenic cells can remyelinate the damaged axons and restore function. Cells can be obtained from multipotential stem cells, which have been expanded and commited to oligodendrocyte lineage before transplantation. ES cell-derived oligodendrocyte precursors were transplanted into a rat model of myelin disease. The cells efficiently myelinated axons in both the brain and spinal cord but did improved neurological function in these animals (Liu, 2000).

The derivation of neural progenitor cells from human embryonic stem (ES) cells is of value both in the study of early human neurogenesis and in the creation of an unlimited source of donor cells for neural transplantation therapy. In our Institution Hadassah Medical Center in Jerusalem, the generation of enriched and expandable preparations of proliferating neural progenitors from human ES cells was obtained. The neural progenitors could differentiate in vitro into the three neural lineages, astrocytes, oligodendrocytes, and mature neurons. When human neural progenitors were transplanted into the ventricles of newborn mouse brains, they incorporated in large numbers into the host brain parenchyma, demonstrated widespread distribution, and differentiated into progeny of the three neural lineages. The transplanted cells migrated along established brain migratory tracks in the host brain and differentiated in a region-specific manner, indicating that they could respond to local cues and participate in the processes of host brain development (Bjorklund 2002).

Spinal Cord Damage

Spinal cord injury is a major source of morbidity following trauma. Degenerative diseases of the spinal cord, often lead to premature death. Mouse ES cells have been grafted into the injured spinal cord of immuno suppressed rats. Surviving cells developed into neurons, oligodendrocytes and astrocytes and supported partial recovery of motor function in the hind limbs that were affected by the spinal damage. However, no clinical trial has demonstrated significant functional effects of grafting primary embryonic neural tissue to the spinal cord in humans (Reubinoff, 2001).

Parkinson's disease

Parkinson's disease is due to degenerative changes in the ventral midbrain causing a striatal dopamine deficit and a severe movement disorder. Parkinson's disease so far is the only disorder that has been treated successfully with transplantation of embryonic brain tissue. A limitation for embryonic brain tissue neural transplantation trials in Parkinson's disease is the need to use multiple donors for each patient. In future to use a stem cell that could be proliferated in an unlimited fashion and then differentiated into a dopamine-producing cell with a full repertoire of neuronal features may be a curative approach. Recently, undifferentiated mouse ES cells were found to develop into fully differentiated dopamine neurons after transplantation into a rat experimental rat model (Lumelsky 2001).

Diabetes

Diabetes, which affects millions of people in the World, results from abnormal function of pancreatic islets. Current diabetes drug therapies do not provide sufficiently tight control of blood glucose to avoid late-stage complications. Transplantation approaches using the whole donor pancreas or isolated islet-cell transplantations are limited by a shortage of donors, major surgery and long-term immuno-suppression. Lumelsky and coworkers succeeded in generating cells that produce insulin and other pancreatic endocrine hormones from mouse ES cells. When injected into diabetic mice, the insulin-producing cells undergo rapid vascularization and maintain a clustered, islet-like organization (Drab, 1997).

Cardiovascular Disorders

Cardiovascular Disorders with its effects upon the brain, heart, kidneys, other vital organs, and extremities, are the leading causes of morbidity and mortality in Western countries.

Transplant of healthy heart muscle cells could provide new hope for patients with chronic heart disease

whose hearts can no longer pump adequately. The goal is to develop heart muscle cells from human pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the failing heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and work together with the host cells. Experiments carried out in Isreal show that human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. The human ES cell-derived cardiomyocytes displayed structural and functional properties of early-stage cardiomyocytes. Establishment of this unique differentiation system may have significant impact on the study of early human cardiac differentiation, functional genomics, pharmacological testing, cell therapy, and tissue engineering (Kehat, 2001).

Cancer Research and therapy

The major treatment strategy for cancer patients has been to kill the tumor cells by radiation or chemotherapy, an approach that is effective for some types of cancer, but not for others. Human stem cells experimentation may be important to cancer research. Stem cells may be used to treat the tissue toxicity brought on by cancer therapy. The isolation and characterization of stem cells and in depth study of their molecular and cellular biology may help to understand why cancer cells survive despite very aggressive treatments. Once the cancer cell's ability to renew itself is understood, new therapeutic strategy may be introduced for prevention and treatment of this common and lethal condition.

Additional degenerative conditions, and disabilities like, osteoarthritis and rheumatoid arthritis and others may be treated in future applying this new therapeutic approach.

Future Research

The use of stem cells for therapeutic purposes has been proposed for many different diseases. However basic research is still needed before translation of present experimental evidence of basic research to clinical trials. It is important to determine the best conditions for growing the cells and directing their differentiation into specialized cells, such as neurons, muscle cells, and insulin producing cells. Investigators will also need to learn about some of the key genes that control the capability of an embryonic stem cell to proliferate in an undifferentiated state. Research is needed on some of the existing cells lines regarding safety testing in culture and in animal model systems. Before stem cells (ES) for transplantation can be clinically applied, the well-known problem of immune rejection must be overcome. The human stem cells derived from embryos created by In vitro fertilization (IVF) would be genetically different from the recipient. Research using human embryonic stem cells will also facilitate the development of approaches to avoid immune rejection of transplanted cells, as well as their integration into and ability to survive in target tissue.

Israeli scientists have been at the forefront of ES cell research. They were key players in the landmark isolation of stem cells from human embryos in 1998. And of the first 12 publications on human ES cells, 10 included Israeli authors (vogel, 2002).

Human embryonic stem research and its potential clinical application is a hope for new modalities of treatment especially for elderly generation suffering of degenerative medical conditions. Since at present time the research involves the use of early embryos that are destroyed in the process, the research is inextricable linked with the abortion debate in most countries. The use of human stem cells raises many ethical issues, for example: the moral status of the embryo, the consents required to use embryonic stem cells and other genetic material, genetic privacy and ownership of genetic information. Therapeutically orientated research on embryos was banned by some individual couple, some societies and religious authorities. For many people, embryos have intrinsic value from the moment of conception, whatever their stage of development, wherever they are, and whatever their likely future. It does not matter that the embryo might be one of several hundred thousand left over after IVF and waiting almost inevitable discard.

Roman Catholic doctrine holds that embryos have intrinsic value (Catholic Church, 1987). The Pope publicly expressed his disapproval of human stem cell research.

Conclusions

The 21st century may well be the century of the life sciences, and major developments and improvements in medicine and human health are expected from the extraordinary progress are making in our understanding of biology. One aspect is regenerative medicine, that is, the scientists of replacing degenerated or damaged tissue, and thereby curing numerous diseases that are possibility intractable. Stem cells are the tools central to this unprecedented approach to therapy. They currently are cells with the intrinsic ability to develop into a diversity of new tissues and thereby replace or repair the diseased, damaged or dysfunctional organs in the patient.

The only source of human stem cells is the human body itself-adults, fetuses, embryos or umbilical cord. The origin of the material required to develop new clinical applications raises a variety of complex issues.

Scientific research on stem cells and therapies involving their use raise questions concerning the ethics of obtaining these cells, the liberty of research, the basis of patenting, and the morality of manipulating human tissues in this way.

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