REVIEW

Biomedical and social contributions to sustainability

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Over the past two or three centuries, biomedical advances have provided methods to prevent and treat infectious diseases. These changes have greatly reduced human suffering and enhanced sustainability by allowing people to live longer and healthier lives. The challenge for the coming centuries will be to ensure that these longer, healthier lives are also more productive lives. We must build on the gains of the past by translating new discoveries in regenerative medicine into therapies for degenerative and genetic diseases. Stem cells may be used to identify drugs that prevent the development of symptoms or to replace cells that have either died or lost their physiological function. In the case of genetic diseases, it may be possible to correct the genetic error. While most conditions that might be treated in these ways are common to all communities, some are more prevalent in specific races. Provision of these and other benefits depends not only on attainment of the research objectives, but also upon our ability to make treatment opportunities available throughout both developed and developing communities. The long history of researching and treating infectious diseases shows that it may take many decades to reap the full benefit of the new biological understanding.

Keywords: biomedical; sustainability; infectious disease; gene therapy;
stem cells; degenerative disease

1. Introduction

Over the past 250 years, our ability to prevent and treat infectious diseases has transformed human lifespan and lifestyles. One measure of the effect of improved public health is the estimate of lifespan at different times and in different countries. Although this approach has significant limitations and must be considered cautiously, the statistics are remarkable. During that 250 year period, average human lifespan has more than doubled. At the present time, global average lifespan at birth is over 80 years in some countries. As far as can be judged, lifespan did not rise significantly above 35 years in any community until the nineteenth century. It is estimated that in 1900, average global lifespan

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at birth was 31 years—or 50 years in rich developed countries. By mid-century, the global estimate was 48 years and by 2005, it was 65.6 years. The recent estimates suggest that life expectancy ranges from less than 50 years in places like Angola, Democratic Republic of Congo, Guinea-Bissau, Mali, Nigeria and Swaziland to 82 years or more in places like Australia, Italy and Switzerland. A comparison of the birth rates per 1000 of population reveals the dramatic implications of these disparities for human sustainability and population control. In countries where life expectancy is among the highest, the birth rate is among the lowest, and vice versa (table 1). Obviously, wealth, education, religion and access to contraception figure into the differences. However, better public health also means that families have a reasonable expectation that their offspring will survive to adulthood, thereby enabling them to make choices to limit the size of their families.

To a considerable extent, the great change in public health reflects a progressively greater ability to either prevent or treat infectious diseases, and there is every reason to expect further progress in this area. In contrast to the advances in the prevention and treatment of infectious diseases, relatively little progress has been made in the treatment of diseases that reflect the death or loss of normal function of a specific population of cells in the body. These diseases include diabetes, motor neuron disease, some forms of sudden heart failure, thalassaemia and sickle-cell anaemia. In some cases, such as motor neuron disease, the pathology reflects degeneration of the cells during the person's life and the symptoms may not develop for several decades. In others, such as thalassaemia, the abnormality is present at birth and these are more properly described as developmental diseases. For the sake of simplicity in this review, the term 'degenerative disease' will sometimes be used to include both types of disease.

The change in the major causes of death at different times reveals that we have become able to prevent death by some infectious diseases [1]. In the past, a considerable proportion of children died within the first 5 years of their life as a result of infectious diseases, such as measles and whooping cough. This pattern was so clear that these and other diseases were commonly known as 'childhood diseases'. In developed countries, such as the UK, the vast majority of children avoid these diseases if they are vaccinated appropriately. However, infant mortality remains troublingly high in countries that have not yet been able to establish effective systems for healthcare. In richer countries where these precautions are now taken, childhood deaths are far less frequent and average life expectancy has increased accordingly. In these countries, the major causes of death are different, with far greater incidence of degenerative diseases such as cardiovascular disease, stroke, diabetes and cancer. There is also a greater incidence of mental and neurodegenerative diseases. These changes being associated with an ageing population as a consequence of increased longevity and also altered lifestyle.

At the present time, research continues to seek treatments for emerging infectious diseases. Moreover, for the first time, emerging techniques in stem-cell biology and molecular genetics have raised the prospect of being able to understand and ultimately treat degenerative diseases. These will make it possible in the near future to produce, routinely and in large numbers, cells from different tissues of a particular patient either for study in the laboratory or for the use to

Table 1. Average lifespan estimated in 2008 Human Development Index Country Ranking, Human Development Report 2009 (http://hdrstats.undp.org/). 2009 Birth Rate per 1000 Population (http:// www.indexmundi.com/g/r.aspx?v=25.Z). Countries in bold type are referred to in the text.

country	average lifespan (years)	human development index rank	birth rate per 1000 population
Angola	**46**	**143**	**43.69**
Australia	**82**	**2**	**12.47**
Belgium	80	17	10.15
Benin	57	161	39.22
Canada	81	4	10.28
Congo	**54**	**136**	**42.63**
Denmark	79	16	10.54
Dominica	74	73	15.73
Equatorial Guinea	53	118	36.52
France	81	8	12.57
Gambia	59	168	37.87
Greece	80	25	9.45
Guinea-Bissau	**49**	**173**	**37.95**
India	64	134	21.76
Italy	**82**	**18**	**8.18**
Kenya	54	147	36.64
Liberia	54	169	42.25
Luxembourg	80	11	11.73
Mali	**49**	**178**	**49.15**
Malta	80	38	10.36
Mozambique	51	172	37.98
New Zealand	81	20	13.94
Nigeria	**49**	**158**	**36.65**
Papua New Guinea	62	148	27.55
Republic of Korea	80	26	8.93
Rwanda	58	167	39.67
Singapore	81	23	8.82
Swaziland	**48**	**142**	**26.25**
Switzerland	**82**	**9**	**9.59**
Tanzania	53	151	34.29
Tunisia	75	98	15.42
Uganda	52	157	47.84
UK	80	21	10.65
USA	78	13	13.82

treat either that person or another patient. Molecular tools make it possible to select individual donors either with specific inherited diseases for research use in the laboratory or with the specific genotype that would make them suitable tissues donors to other patients requiring cell therapy. Alternatively, such methods can be used to make precise changes in the genes—again either for research purposes or to make the cells more appropriate for therapeutic use.

Development of measures to prevent and treat infectious diseases depended upon a mixture of basic research, technology development and, most recently, a determination to provide an equal quality of life to all members of the community.

At the end of the eighteenth century, the cause of what we now recognize to be infectious diseases was not understood. There were no systematic methods for immunization, nor were any of the modern antibiotics available. The need to dispose of sewage carefully and provide clean water was not generally recognized. Sporadic attempts to improve sanitation were not implemented effectively. The sequence of events that brought us from this situation to the present position is complex and involved contributions from many different people who are too numerous to mention. However, a brief summary will provide an indication of the unpredictable nature of the process and the prolonged time scale involved. This may suggest the way in which the innovative treatments in regenerative medicine that are envisaged at present will be developed. It will also emphasize the effect of social inequality upon health and the importance of social action to ensure that existing and new treatments are made available to everyone in the world as quickly and effectively as possible.

2. Control of infectious diseases

Use of immunization, development of a basic understanding of the nature of infectious disease, research into effective methods of preventing sepsis and the ability to counteract specific infections all intertwined to bring about major advances in the control of infectious diseases.

(a) Immunization

Many distinguished researchers working in different parts of the world contributed to the development of the array of vaccines that are available today. The earliest form of immunization, used to treat diseases such as smallpox, has been practised for more than 1000 years. This involved the introduction of pus from an infected person or an animal through small holes in the skin of the person being treated. This approach was apparently widespread in many parts of Asia, Europe, Africa and North America, but late in the eighteenth century, it was made more methodical by several people in different countries [2]. In Britain, Edward Jenner took the process a stage further in 1792 by making a systematic investigation and using infection in cows to provide protection in humans. Building on Jenner's work, almost 200 years later, smallpox was eradicated from the human population by a large-scale programme of immunization [3].

Perhaps, the most paradigmatic of these stories is the history of the polio vaccine. It is hard for us to envisage now, but in early twentieth-century polio, the occurrence of periodic epidemics made polio a terribly frightening disease [4]. During the first half of the twentieth century, there were epidemics in many parts of the world that involved hundreds of thousands of cases and caused tens of thousands of deaths. It is also estimated that there are some 20 million polio survivors in the world today, many of whom still suffer aftereffects [5]. Many well-known people from all walks of life were victims of this disease, including US President Franklin Roosevelt. A National Foundation for Infantile Paralysis was established by President Roosevelt and his former law partner, Basil O'Connor. Today the organization is known as 'The March of Dimes' after one of the annual fund raising events, and it supports research into a number of diseases.

In 1955, this organization had US $67 million available for research on polio, which it tapped into to fund a large trial of polio vaccines. Jonas Salk in that same year introduced the first effective vaccine against polio after years of dedicated research. Salk became a national, indeed an international, hero when the availability of an effective vaccine was announced. The Salk vaccine used an inactive virus, whereas Albert Sabin introduced a live vaccine, which was the result of experiments with more than 9000 monkeys and 100 chimpanzees. From this research, Sabin isolated a rare form of poliovirus that could reproduce in the intestinal tract, but not in the central nervous system. This vaccine was licensed in 1962 and is still used worldwide [6].

Salk is without doubt the best-known developer of vaccines. However, American microbiologist Maurice Hilleman is credited with developing more vaccines than anyone else, though his name is unknown to the general public [7]. Of the 14 vaccines routinely recommended in current practice, he developed eight: measles, mumps, hepatitis A, hepatitis B, chickenpox, meningitis, pneumonia and infections of the lower respiratory tract caused by haemophilus influenzae in young children. He also developed the MMR vaccine for measles, mumps and rubella in the first vaccine to mix live viruses.

During the last 25 years, several organizations have taken advantage of the ability of effective vaccines to launch major health campaigns. In 1974, the World Health Organization (WHO) established a programme of immunization at birth against six diseases: tuberculosis, polio, diphtheria, tetanus, whooping cough (pertussis) and measles. Subsequently, the United Nations Children's Fund (UNICEF) worked with WHO to promote universal childhood immunization. In 2000, the Global Alliance for Vaccines and Immunization (GAVI) was established to strengthen routine vaccinations and introduce new and under-used vaccines in countries with a *per capita* gross domestic product of under US$1000. GAVI is now entering its second phase of funding, which will last through 2014. While a very large proportion of children are immunized each year (82% in 2008), this still means there are many millions who are not [8].

The development of these successful vaccines involved the introduction of a number of technical innovations, and the search continues for new opportunities. At present, the use of DNA vectors is offering hope of being able to develop effective immunization strategies for human immunodeficiency virus (HIV) and malaria. However, above all else, it depends upon accurate understanding of the nature of the infective agents.

(b) Causes of infection and development of aseptic techniques

Key to all of the current research is an understanding of the nature of the infections. At the time of the first successful immunizations, the nature of the infectious agent was not well understood. Working in Delft in The Netherlands and using microscopes that he made himself, Anton von Leeuwenhoek is believed to be the first person to actually see micro-organisms. He corresponded with members of the Royal Society of London about the organisms' structure, and his early results were published in 1673 by that Society. A detailed account of his work is provided by Porter [9].

A number of individuals working in different contexts noted that infection occurred in specific circumstances and spread in a predictable manner. They then drew the conclusion that infectious agents were the cause of the disease and

introduced aseptic techniques. In 1847, Ignaz Semmelweis, working in Vienna, noticed that post-partum death of women was far more common among women who were attended by doctors or students than among those attended by midwives. Semmelweis noticed that doctors had often come straight from an autopsy and suggested that doctors should wash their hands in chlorinated lime water before examining pregnant women. As a result, death among women in his hospital was reduced dramatically [10,11]. In this case, the value of the new approach was not immediately recognized or widely adopted. Semmelweis died young, aged 47, in an asylum.

The physician John Snow, working in London during the cholera outbreak in 1854, noticed that the occurrence of cholera was associated with people who used a specific well [12]. Using pioneering statistical and epidemiological methods, Snow argued convincingly (though did not definitively prove) that the disease was transmitted through a waterborne pathogen. This contradicted the prevalent 'miasma' or 'bad air' disease models of the time, and gave public officials a greater ability to target the sources of such outbreaks.

Formal proof of what is now described as the 'germ theory of infectious disease' was provided by Louis Pasteur and Robert Koch. (Details of the experiments conducted by these two innovators are provided by Ullmann [13]). Pasteur demonstrated that no bacterial growth occurred if air was prevented from reaching broth that had been boiled. By contrast, if air was allowed to reach the broth, growth occurred. These experiments, carried out between 1860 and 1864, provided convincing evidence that life did not develop spontaneously, but rather was carried in the air. In 1890, Koch published a precise set of tests that must be completed to provide the formal proof that a specific agent was responsible for a disease (for an up to date review on the subject, see Fredericks & Relman [14]). Summarized briefly, these require that: the agent must be found in the tissue of all organisms suffering from the disease; it must be isolated from the diseased organism and grown in a pure culture; it must cause the disease if introduced into a healthy organism; and finally it must be reisolated from the infected organism. These broad principles are still accepted, although it is appreciated that there are exceptions, such as individuals who carry the infective agent without developing disease symptoms.

Another innovator was Joseph Lister in Glasgow. When he took the position of Regius Professor of Surgery at Glasgow, he assumed responsibility for a surgical ward in a new building. He found that between 1861 and 1865, 45–50% of his amputation patients died from sepsis. Lister was aware of the results of the work by Pasteur, and at this point, he introduced steps designed to prevent microbes from entering the wound, including the use of carbolic acid. In 1867, he reported to the British Medical Association that there had been no sepsis in the ward during the previous nine months after the new sanitary measures were put into place [15].

(c) Antibiotics

There is a long history of using specific extracts or compounds to assist in recovery from infection or repair of damaged tissue. It is reported that extracts of plant material have been used to treat what we would now recognize as

infected tissue for thousands of years in locations as diverse as China, Egypt and Greece. A more systematic search for beneficial compounds followed upon the recognition of the nature of infections. Broadly, there are two different approaches, either to synthesize chemicals that are able to kill bacteria or to identify active extracts of plant or fungal tissue. Both have made significant contributions to medicine and earned their pioneers major awards, such as the Nobel Prize.

At an early stage in his career, German researcher Paul Ehrlich developed a passion for the use of dyes to study tissues and infectious agents (as recorded in the biographical note by Bosch & Rosich [16]). Some of his reagents and protocols are still in use today. During this work, he noticed that with some dyes, there are differences in the extent to which they bind to different animal (including human) tissues and bacteria. On the basis of that observation, over a period of years he synthesized and screened many different compounds to find stains that kill bacteria without harming the animal tissue. He also established the concept that it might be possible to infect animals with bacteria that cause diseases in humans and so used those animals to assess the effectiveness and safety of new compounds in treating the disease, rather than treating humans directly. Building on the earlier identification of *Treponema pallidum* spirochete as the causative agent of syphilis by Fritz Schaudinn and Erich Hoffmann, Ehrlich introduced Salvarsan, a drug that was effective in treating syphilis. As the effect of syphilis at that time was comparable with that of acquired immune deficiency syndrome (AIDS) today, the importance of this achievement can readily be imagined.

In 1877, after Louis Pasteur observed that airborne organisms inhibited the growth of anthrax bacillus, he was among the first to make the point that it might be possible to take advantage of the fact that some micro-organisms produce material that is harmful to bacteria [17]. This effect was observed independently by several others including Alexander Fleming in 1928. Fleming was able to define some of the characteristics of the fungal product that had this effect, but it was only 10 years later that Howard Florey and Ernst Chain were able to isolate the active principle. The outcome of their efforts, penicillin, was particularly important because it is active against a wide range of different bacteria and has very limited adverse effects. The evidence that beneficial chemical compounds could be produced in great quantity and used widely stimulated the research that has led to the production of a large number of different compounds. For their combined efforts, Fleming, Chain and Florey shared the Nobel Prize in 1945 [18].

The four threads of research concerned with immunization, antibiotics, asepsis and the basic biology of infection have certainly come together to provide great advances in healthcare, but inspection of the summary chart reveals that progress in these four areas has been haphazard (table 2). Sometimes a major advance has depended upon an empirical study to reveal and define new opportunities, as was the case when Jenner and his contemporaries promoted immunization by introducing pus from infected animals to protect humans against smallpox. In other instances, acute observation has revealed important understanding that became the basis of systematic analysis, as was the case when Semmelweis observed that doctors coming from autopsies to the delivery room were causing sepsis in women at childbirth.

Table 2. Key events in the development of our ability to control infectious diseases.

date	basic biology	immunization	asepsis	antibiotics
Up to 1675	1673 Von Leeuwenhoek *micro-organisms*			
1700				
1725				
1750				
1800		1792 Jenner *smallpox*		
1825				
1850			1847 Semmelweis *chlorine wash*	
1875	1864 Pasteur *germ theory*		1854 Snow *cholera*	
			1867 Lister *infection control*	
1900	1890 Koch *germ theory*			1877 Pasteur *antibiotics*
1925				
1950				1928 Fleming
				1945 Florey and Chain *penicillin*
1975		1955 Salk *polio*		
		1950s–1960s Hilleman *vaccines*		
2000		1974 Global Alliance *mass vaccination*		
2025		2008 82% children immunized		

3. Degenerative and developmental diseases

Whereas most of the progress in the treatment of human disease that has been achieved so far has been concerned with infectious disease, new developments in regenerative medicine have the potential to provide effective treatments for many diseases that reflect death or loss of normal function of cells. There are a number of ways by which stem cells may be used to provide new treatments for these diseases. They may be used for research in the laboratory to identify drugs that delay or prevent the degeneration. Alternatively, drugs may be sought that are able to produce stem cells within the body to multiply and migrate to the site of injury. Finally, derivatives of stem cells may be transplanted into the patient to replace cells that have either died or lost their physiological function.

(a) Candidate diseases

While most conditions that might be treated in these ways are common to all communities, some are more prevalent in specific races. One such family of diseases is the group of haemaglobinopathies. These genetic diseases of red blood

Table 3. A comparison of the advantages and disadvantages of different stem-cell populations.

stem-cell population	source	advantages	disadvantages
embryo	embryo at early blastocyst stage	grow for prolonged periods in culture	limited availability
		able to form all adult tissues	genetics not known in advance
			teratoma formation
			social concerns
foetal	tissue of aborted foetus	can study mechanisms in development	social concerns
			limited availability
		source of differentiated cells for therapy	cells may have reduced growth potential
adult	many different tissues	selected genotype	limited ability to form different tissues
		study inherited diseases	reduced growth potential
		use for autologous therapy	
iPS cells	treatment of adult cells, e.g. skin	selected genotype	teratoma formation
		study inherited diseases	need confirmation of physiological normality
		use for autologous therapy	
		grow for prolonged periods in culture	
		able to form all tissues of adult	

cells include sickle-cell anaemia and thalassaemia. Strategies are being developed to provide a means of correcting the genetic cause of more severe cases through production and genetic modification of stem cells that would be returned to the patient. All of these approaches depend upon our developing the ability to isolate and maintain stem cells and their derivatives in such a way that they can be studied extensively in the laboratory and in some cases be transferred to a patient.

(b) The nature of stem cells

All stem cells have the characteristics that when they divide, they are able to give rise either to more cells like themselves or a different daughter cell type. In this way, they are first able to establish a tissue during development and then to maintain the tissue during adulthood.

Until very recently (2005), stem-cell population were considered as belonging to one of two broad categories. One of these categories is made up of stem cells derived from tissues, and these are generally known as adult or tissue stem cells. The other category of cells is usually derived from preimplantation embryos, and these are known as embryo or pluripotent stem cells. The advantages and disadvantages of each type in regard to their use in research or therapy are summarized in table 3.

(c) Adult stem cells

In general terms, adult stem cells have a relatively short life and are only able to form types of cell that are normally present in the tissue from which the stem cells were obtained. However, there is an extensive search for adult stem cells that do have the ability to form a wider range of different cell types or alternatively for a simple means of giving them that ability. Adult-derived cells have the advantages that they may be transferred without immune rejection either to the donor or to other genetically very similar individuals and that the genotype of the cells can be known in advance. In addition, they can be used to study inherited disease carried by the donor of the cells. Leukaemia is a striking example of a genetic (and in some cases inherited) disease of adult stem cells that has been studied extensively.

There are a number of treatments that take advantage of stem cells in adult tissues. Bone-marrow transplantation—used to restore the production of blood cells in patients with certain types of anaemia or immunodeficiency, or following chemotherapy to treat cancer—depends upon the presence of haematopoietic stem cells in the marrow for their effect. In experiments with mice, it is possible to restore the immune system of an animal by the transfer of a very small number of selected stem cells (e.g. [19]). In recent years, bone-marrow cells have been transferred into patients with diseases of a variety of tissues including the liver and heart. In some cases, there was a modest benefit [20–22]. It was suggested that this might reflect an ability of haematopoietic stem cells to differentiate into cells of the tissue being treated (liver or heart, respectively). Indeed, there is some evidence of a very rare conversion in some patients and experimental animals, but that this usually involves fusion between a haematopoietic cell and a hepatocyte [23]. However, the general consensus now is that the great majority of the benefit reflects an ability of immune cells present in the marrow to modulate the inflammatory response [24].

The presence of stem cells in the skin makes it possible to grow sheets of tissue that can be used in the treatment of burns to provide an initial cover. Skin is a complex tissue with several functions and many different cell types. However, in a clinical emergency, the urgency is to provide a layer of cells that can limit infection and prevent loss of body fluids, and for this purpose, even an imperfectly grown tissue is valuable [25,26]. Recently, cosmetic and pharmaceutical companies have begun to use laboratory preparations of cells from the skin to assess the safety of their preparations.

An understanding of the nature of the stem cells in different tissues of an adult is also required for the development of protocols for the differentiation of embryo-derived stem cells. This is important for two very different reasons. While stem cells derived from the embryo, and others with similar characteristics, have considerable advantages that will be discussed below, they have the great disadvantage that they may form potentially dangerous tumours called teratomas if transplanted into an adult. The availability of tissue stem cells in the laboratory makes it possible to establish optimized culture protocols and define their characteristics. Antibodies prepared during this work can be very useful during the derivation of tissue cells from embryo-derived stem cells. In addition, knowledge of patterns of gene expression in tissue stem cells is important when making quality assessment of cells.

(d) Embryo-derived stem cells

When cultured in appropriate conditions, embryo-derived stem cells may be grown in the laboratory for prolonged periods of time while retaining the ability to form all of the different tissues that make up an adult. At present, none of the protocols are able to direct all of the pluripotent stem-cell populations to the desired differentiated cell type. However, the mutability of embryo-derived stem cells provides researchers with invaluable opportunities to analyse the mechanisms that regulate differentiation in normal development and to establish protocols, which may then be used to induce differentiation of pluripotent stem cells to specific tissue types.

The great limitations of embryo-derived stem cells are that the genotype cannot be selected in advance and that pluripotent stem cells have the ability to form teratomas if transferred inadvertently into patients during cell therapy. This risk, along with the limitations of current differentiation protocols, limits the use of derivatives of pluripotent cells in cell therapy.

(e) Induced pluripotent stem cells

The Japanese scientist Shinya Yamanaka pioneered a method, now widely used, to change a small proportion of adult cells into cells that are very similar to embryo-derived stem cells. This is achieved simply by the introduction of four or five key proteins. Cells obtained in this way are known as 'induced pluripotent stem cells', or iPS cells. In the initial protocols, retroviral vectors were used to introduce the key proteins, but more recently, a number of different approaches have been used. These include a variety of other vectors, direct introduction of the key proteins or of small molecules that may act by inducing expression of the same genes.

Whichever approach is taken to derive iPS cells, a number of points appear to apply. First, 'reprogramming' of gene expression is a slow process, typically taking between one and two weeks for the pattern of gene expression to become similar to that of embryo-derived cells. Secondly, only a small proportion of cells are reprogrammed to a pluripotent state. Third, there are reports of greater variation between iPS cell lines than between embryo stem cell lines from the same embryo, a variation that in some cases is associated with differences in the residual memory of the molecular mechanisms responsible for maintenance of the donor tissue functions. It is to be expected that over the next few years, the methods for producing iPS cells will be refined, become more reproducible, and for many purposes iPS cells will become the stem cells of choice.

Just as is the case for embryo stem cells, the great value of iPS cells is that they grow in culture for prolonged periods while retaining the ability to form all tissues. However, they have the great additional benefit that, in principle, they can be produced from any person. This offers unique opportunities in studies of inherited diseases or for the establishment of libraries of cells for transfer into patients. It has been estimated that a relatively modest number of cell lines could establish a library of cells that are able to provide a reasonable immunological match to a considerable majority of patients within a particular community [27]. However, iPS cells have the same inherent risk as any other pluripotent stem cells, that they could form teratomas if inadvertently transferred into patients.

(*f*) *Direct reprogramming*

Another means of deriving stem or progenitor cells is being investigated at present, but the value of the approach is not yet clear. iPS cells are produced by the introduction of transcription factors that are involved in the maintenance of pluripotency. In an analogous approach, differentiated neurones were produced by the introduction of transcription factors involved in neuronal function into murine skin cells. The opportunities and limitations of this approach remain to be revealed. In this first experiment, the cells produced were terminally differentiated and so unable to divide. There would be some advantages in producing progenitor cells, which do have the potential to multiply. While they are able to form a variety of different cell types, whether the risk that they would form teratomas if transferred into patients is less than if pluripotent cells are transferred remains to be confirmed.

4. Biomedical uses of stem cells

Much of the writing on the clinical use of stem cells and their derivatives has focused upon their potential use in cell therapy to replace cells that have died or ceased to function normally. This is despite the fact that cell therapy is very challenging, among other reasons, because of the extraordinarily difficult requirement that only high-quality cells of a selected tissue type should be transferred into patients. In addition, the number of cells required for a treatment would be many more than could be produced by the small-scale procedures that are used in laboratory research. There is a danger that a premature focus upon cell therapy overlooks the considerable benefit that is already available from the use of stem cells for drug discovery.

(*a*) *Drug discovery*

The availability of stem cells from patients who have an inherited condition and from closely related donors who do not have the condition enables laboratory studies of both normal development and development that is perturbed by genetic disease. In turn, this provides the information that is required to search for drugs that are able to prevent the symptoms of the disease. Drug development in this way depends upon large numbers of cells from diseased-affected tissue being available in the laboratory over a period of years. In some cases, such as motor neuron disease, two cell types are affected: motor neurones and astrocytes, and these must be grown in co-culture. While it is desirable to have pure cultures of the affected cell types, the consequence of having other cell types present during research or drug development may be less than that if inappropriate cells are transferred into patients. While some conditions may be studied in adult stem cells, this is not often the case because cells such as cardiomyocytes or neurones cannot be obtained from the patient in sufficient number. It is in these circumstances that iPS cells are already making a considerable contribution.

Familial dysautonomia (FAD) is an example of a disease that has been studied by iPS cell production [28]. This rare disease is associated with the death of peripheral and autonomic neurones, but neither the pathogenesis nor the specificity of this cell death are understood. There are no mouse models of the

disease. Patients with this autosomal recessive disease have a point mutation in the I-k-B kinase complex-associated protein (IKBKAP) gene, which results in a splicing defect and reduced levels of normal IKAP protein. In one study, researchers compared the level of normal transcript in control and FAD cells that had been induced to differentiate into five different tissues representing all three germ layers, and in all cases, the level was significantly lower in the FAD cells [28]. They were then able to use this as a model system to screen for molecules that could have therapeutic potential and they identified the first compounds that were able to increase levels of normal IKAP protein.

These studies provide proof of the principal that it is possible to use iPS cells from patients with inherited diseases to study disease pathogenesis and, in some cases, to identify candidate drugs to treat the disease. However, different challenges may become apparent with other diseases. FAD appears to be cell autonomous so that it is only necessary to study the affected cell type. By contrast, development of the symptoms of motor neurone disease associated with mutation in the superoxide dismutase 1 (SOD1) gene depends upon influences of the causative mutation in both motor neurones and glia. The non-cell autonomous nature of the disease was demonstrated in transgenic mice [29], and studied in tissue culture of cells derived from embryo stem cells carrying the causative mutation [30,31]. In these latter studies, it was found that anti-oxidants were able to ameliorate the effects of mutant glia [31].

Secondly, the symptoms of many degenerative diseases only become apparent in mature or elderly people. It seems unlikely that the harmful changes associated with the disease will emerge during tissue culture that will only last a few weeks. In the studies of motor neurone disease already referred to, the effects were only apparent if the level of expression of the mutated gene was increased [30]. Nevertheless, differences in pattern of gene expression in cells derived from patient iPS cells may help to identify causative mutations and, at a later stage in the project, provide a means of searching for protective compounds.

(b) Toxicology

Stem cells also have the potential to make drug discovery quicker and less expensive. A major part of the cost of developing new drugs is in the tests that are required to ensure that the compound is safe. In some cases, compounds are withdrawn at a very late stage in their assessment after they are found to have unacceptable side effects [32,33]. In principal, the ability to provide cells of different tissues of known different genotypes could reduce the risk of late withdrawal and so reduce the cost of drug development. Recent research suggests that hepatocytes and cardiomyocytes which would meet the specification required for this use can now be derived from iPS cells. Hepatocytes are required because differences between people in the efficiency of metabolizing drugs may lead to unacceptably high concentrations of the drug in some patients and an adverse reaction to the drug. Cardiomyocytes are particularly important because this cell type may be adversely affected by the drug with potentially fatal consequences.

In a recent report, iPS cell lines were differentiated to hepatic endoderm at efficiencies of between 70 and 90 per cent, using a protocol established in previous research with human embryonic stem cells to mimic physiological conditions during development [34]. These cells expressed the hepatic markers albumin and

E-cadherin, also expressed alpha-fetoprotein, hepatocyte nuclear factor-4a, and a metabolic marker, cytochrome P450 7A1 (CYP7A1), confirming differentiation to a definitive endodermal lineage. In addition, these iPS-cell-derived hepatocytes supported both CYP1A2 and CYP3A4 metabolism, which is essential for drug and toxicology testing.

Two recent studies have confirmed the potential use of stem-cell-derived cardiomyocytes in toxicology. In the first, human embryo stem cells were a source of cardiomyocytes to assess the effect of drugs upon cardiomyocytes in tissue culture. The sequence of events during the contractions of the heart can be monitored accurately and variation may then be seen during specific phases. Analyses of these phases showed dose-dependent responses to 12 cardiac and non-cardiac drugs. Drugs with known effects on the phase of the heart's electrical cycle, called the QT interval, displayed the predicted effect of human embryonic stem-cell-derived cardiomyocytes. The perturbing effect on the cells in culture occurred at the same range of concentrations that the compounds influenced QT interval in patients. The authors proposed that this test might replace some of the preclinical cardiac toxicity screening tests currently used for lead optimization and further development of new drugs [35].

In the second study, cardiomyocytes were produced from patients known to be affected by a long-QT syndrome, which is associated with sudden heart failure [36]. Electrophysiological studies were carried out on cardiomyocytes derived from iPS cells from carriers and controls. Myocytes characterized as resembling those in two regions of the heart, the atrium and ventricle, exhibited a prolonged QT interval recapitulating the difference seen in life. Furthermore, these cells responded in the predicted manner to drugs known to exacerbate or relieve the symptoms.

Taken together, these two studies provide proof of the principle that cells derived from pluripotent stem cells will provide new opportunities to screen candidate drugs at an early time in their assessment and so have the potential to save time and money. iPS cells have the particular advantage that it is easy to obtain lines of selected vulnerable genotype.

(c) Gene therapy

Stem cells, in particular iPS cells, may offer new opportunities to treat inherited diseases. Several prerequisites must be met in order for this to be possible: the causative mutation must be known; it must be possible to obtain iPS cells and correct the mutation; and finally it must be possible to differentiate the corrected iPS cells to the affected tissue type and transplant those cells to an effective site in the patient. The transplantation site need not be the normal location of the cells, but the cells must be able to exert a normal physiological function. Proof of this principle has been provided in mice for sickle-cell anaemia [37].

Sickle-cell anaemia is one of a number of inherited diseases that includes thalassaemia and affects the functioning of red blood cells [38]. These diseases are particularly prevalent in some races. The precise pattern varies from one disease to another, but in all cases, they are more prevalent in Asian and sub-Saharan African populations, that is, in the less well-developed parts of the world. Approximately, 7 per cent of the world population are carriers of the genes that cause one or other of these diseases, and it is estimated that

300 000–500 000 babies are born with severe forms of such a disease every year [38]. While treatment is possible, each treatment has significant side effects and limitations.

Proof of the principle that it will be possible to treat diseases of the haematopoietic system was provided by correcting a mutation that causes sickle-cell anaemia in mice [37]. The study was carried out in a humanized mouse model in which both γ- and β-globin genes were replaced by human genes. However, the β-gene carried the mutation that causes sickle-cell disease. Mice that are homozygous for this mutation developed typical symptoms including severe anaemia. iPS cells were produced from fibroblasts from the tail tip of such mice. The mutation was corrected by introducing wild-type human β globin.

Corrected cells were introduced into irradiated mice homozygous for the mutation. Detailed studies showed that the corrected cells had engrafted stably, as evidenced by detailed molecular analysis, physiological studies of blood cell populations and clear evidence that disease pathology had been ameliorated. This proof of principle experiment suggests that this approach could be used to treat human haemaglobinopathies, such as sickle-cell disease and thalassaemia.

In principle, it would seem that a single treatment that would offer life-time correction of the disease in a physiological manner would offer great advantages. It would be expensive, but perhaps no more expensive than the total cost of repeated treatment and of the treatment of side effects associated with the use of current treatments.

5. Effect of social circumstances on health of communities

There are profound effects of social circumstances upon individual health, both between different countries and within countries. As noted previously, the standard of healthcare influences the cause of death within a community [1]. It is very disappointing that there are still countries today in which a significant proportion of children fall victim to childhood diseases that have all but disappeared from the developed world. And while far-reaching schemes to improve healthcare in developing countries are now in process, they will require long-term training of nurses and midwives for each community in order to have their full effect.

It is even more shocking that specific areas in developed countries suffer social deprivation to the extent that it has a profound influence upon lifespan. In a study of life expectancy published in 2008, two different areas near Glasgow, Scotland, revealed the profound disparities in life expectancy, even within similar populations. In the economically deprived area of Calton, life expectancy was 54, 28 years less than in the more affluent area of Lenzie, only 8 km away [39]. Similarly, the average life expectancy in London's wealthy Hampstead was 11 years longer than in the less affluent nearby enclave of St Pancras. There is a clear correlation between the human welfare, as measured by literacy and living standards, and human health (table 1).

While there are several analyses that identify an association between differences in lifespan and differences in income, the underlying mechanisms are not clear [40]. It seems likely that there are psychosocial effects in addition to direct effects

through differences in nutrition and healthcare, but recent analyses suggest that in developed countries, there is a negative effect of living in a society with very great differences in income [41]. A most striking finding is that the benefits of greater equality extend to everyone, not just to the poorer members.

6. Conclusions

Advances in public health, including improvements in hygiene and the spread of immunization, have transformed human quality of life and greatly extended average lifespans in much of the developed world. The brief historical summary provided above reveals how the often ad hoc interactions of personalities and ideas contributed to this dramatic improvement over a period of more than two centuries. With the eradication of erstwhile plagues, however, has come a new raft of challenges. Diseases that are associated with these longer lifespans—diabetes, heart disease and the like—push us to find new therapies. Ongoing developments in biomedical research have the potential to make an important contribution to the health and sustainability of human society. In particular, it seems likely that treatments will be developed to control the symptoms or even correct many degenerative diseases. The effect may be to prolong the period of life during which a person is able to make a contribution to his family and community while also enjoying a high quality of life. However, past experience suggests two caveats. First, it may take many decades of halting progress to reap the full benefit of the new biological understanding. Secondly, it seems that the full benefit will only be gained if human communities become more equal.

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