How has the study of rare diseases influenced our knowledge of more common diseases?

Rare diseases can be very frightening for sufferers and their families. When very few people are afflicted with a disease, little may be known about how best to treat it. Policymakers and scientists understandably seek to develop treatments for common diseases which affect large numbers of people such as Alzheimer's disease, heart disease, cancers and diabetes. As a result a substantial amount of research funding goes into discovering more about these illnesses, while rare diseases receive less funding. For example, the National Institute for Health Research, funded by the Department of Health, is providing £5 million per year to a translational research group for all rare diseases[1] , compared to £36 million for a similar group for dementia[2]. However, studying rare diseases can provide insight into the mechanisms of common diseases. One example of this is the disease Hutchinson-Gilford Progeria Syndrome (HGPS, commonly known as Progeria).

Progeria, meaning 'prematurely old'[3] is a disease affecting children which causes them to 'age' extremely rapidly. Children have a normal weight[4] and appearance[5] at birth but they grow much more slowly than other children and quickly start to look 'aged', losing their hair and developing thin-looking, mottled and dimpled skin [6].The most tragic thing about the disease, however, is that it dramatically reduces the sufferer's lifespan and there is no known cure. Affected children die at around 13 years of age from diseases which normally affect older adults, such as heart attacks or strokes[7]. This unusual condition occasionally captures the media's interest, with one patient being described as '*Britain's oldest teen*' and a '*100 year old*' sufferer[8].

HGPS is extremely rare, being estimated to affect 1 in 18 million people. There are currently only 99 sufferers in the entire world[9]. It is a genetic disease which usually arises by chance rather than running in families[10] and comes completely 'out of the blue' for the parents of affected children. Most cases are caused by a genetic mutation which affects nuclear lamina proteins, the 'scaffolding' proteins that give parts of our cells their structure[11]. Patients with progeria suffer from some of the problems that affect normally 'aged' adults, chiefly cardiovascular disease such as heart attacks and strokes, but also hearing loss, osteoporosis and musculoskeletal problems[12]. If we can understand how these diseases arise so rapidly in HGPS children this may shed light on how they develop in the general population.

Over the past decade, as we have begun to understand more about what causes progeria, and about the roles of cells in healthy people, the syndrome has become even more relevant. An especially intriguing discovery is the finding that progerin, the abnormal scaffolding protein which is produced in HGPS, seems to be present in the cells of healthy people as well[13] and seems to accumulate with age[14]. The mutation which produces progerin is the only genetic difference between a progeria sufferer and a healthy baby, causing the dramatic effects and early death seen in HGPS. Could this protein be responsible for ageing in the healthy population, too? Could understanding how we age one day allow us to extend the human lifespan?

Research has previously uncovered the role of parts of the DNA in our cells, called telomeres, in causing ageing. These get shorter as cells grow and divide and after a while they seem to trigger mechanisms that 'switch off' the cell, thus acting as a sort of 'ticking clock' which counts down the cell's lifespan[15]. When enough cells die, our tissues become unhealthy, which may cause problems such as artery disease seen in both progeria sufferers and the older population[16]. It has recently been found that progerin could contribute to this process by damaging telomeres, causing the cell to die earlier[17]. This may be part of the explanation for why progeria sufferers have such a short lifespan. Could we, in the future, find a way to stop the production of progerin? This would be an incredible discovery for the sufferers of HGPS and their families, but perhaps this could also help us to combat some of the common diseases of ageing seen in the general population.

In 2012, ischaemic heart disease was the biggest cause of death in the world[18]. Heart attacks and strokes are often caused by atherosclerosis, fatty deposits in arteries which accumulate over a lifetime[19]. We know that risk factors for cardiovascular disease include high cholesterol, high blood pressure and smoking[20], but progeria sufferers are not exposed to these risk factors. If we can understand how heart disease and strokes develop so quickly in these children despite the lack of risk factors it might be able to tell us a lot about how these develop in healthy adults, and how we can prevent this from happening. Researchers have found damaged areas on the inside of blood vessels in HGPS patients that appeared similar to the 'normal' fatty changes seen in older people's arteries. However, they also found that the outer layer of the artery was unusually stiffened and thickened, causing the vessel to be less stretchy, and in healthy patients this occurs to a lesser extent than was found in the progeria patients. The researchers noted that the same factors they identified as causing this stiffening in HGPS could also contribute to changes which occur with ageing in normal arteries[21].

Another interesting element of HGPS is the fact that patients develop only some of the common diseases which normally affect older people. They don't develop dementia[22] which is estimated to affect 20% of patients over 80 and 70% of patients over 100[23]. There is currently a lot of interest in discovering more about potential treatments for dementia, as with a growing elderly population the number of sufferers is set to double over the next 20 years[24]. Discovering why dementia does not occur in progeria sufferers compared to older adults may help us to rule out some mechanisms, such as progerin accumulation, as causes of it. Another common disease which is not increased in HGPS sufferers is cancer[25] which one-third of us are expected to suffer from during our lifetime[26]. There is a significant increase in cancers between the ages of 40 and 80[27]. Can studying HGPS tell us anything about the mechanisms that cause cancers in the general population? One group of researchers has found that the lack of cancers in HGPS could be due to the death of stem cells, which may help us to further understand the role of stem cells in causing cancers in otherwise healthy people[28]. In addition, HGPS patients do not suffer from high cholesterol, type 2 diabetes or cataracts, other common ailments of older adults, so these are areas which could also be further explored[29].

HGPS is an extremely rare and devastating disease, but research into its mechanisms could give us information about extremely common problems such as heart disease, strokes, cancers, dementia, diabetes, high cholesterol and osteoporosis. This is just one example of a rare disease which is worth investigating not only for its own sake, but also for the enormous amount it may tell us about the mechanisms underlying other common diseases which affect so many people in the general population.

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