A Race Against Time:
An Overview of Progeria and its Clinical Symptoms

Kyle Davis

Writer's Comment: A fellow classmate, involved in some aspect of Hutchinson-Gilford Progeria Syndrome research, introduced me to the rare genetic disorder. Its curious manifestation and developmental peculiarities immediately captured my interest. Much remains to be discovered about the disease, but until recently, its scarcity provided little impetus for further study. This of course made research a challenge. In treadmill-like fashion, it seemed the further I delved into the subject, the more questions I developed. This paper helped me to sift through the stacks of fragmented research, to concisely present HGPS and its potential for additional study, as well as its relevance to the afflicted and healthy alike.

—Kyle Davis

Instructor's Comment: My Writing in the Sciences (UWP 104E) class challenges the idea that writers are born, not made—it takes more than just a way with words to communicate with clarity and grace. When Kyle entered my class, he wanted to improve his technical writing skills. This essay—in response to the final assignment in 104E—shows both his growth as a writer and his ability to make a medical concept clear and compelling. In this piece, Kyle explores a disease that affects just 42 patients worldwide, but receives disproportionate research funding. Progeria causes rapid aging in children, and, as Kyle shows us, it provides a unique view of the aging process that might lead to medical interventions that can stop or retard aging. No wonder this disease is studied so intently. Kyle's ability to communicate medical concepts in a compelling way will serve him well as he pursues his M.D. at UC Davis this Fall.

—Shannah Whithaus, University Writing Program

The idiom goes, "With age comes wisdom," but this is only a partial truth. Had the intellectual who proclaimed this waited another 40 years, he might have instead stated, "With age comes wisdom and possibly success, followed by a certain decline in health, waning looks, and eventually the dulling of one's mind." Today, and for millennia past, an individual's biological clock has seen to it that this progression remains a verity. Although admirers of George Clooney might disagree, given enough time even the best aged wine will sour. Yet we live in a society which can launch men to the moon, can visualize and split atoms, and can transmit invisible waves through the air to be unscrambled thousands of miles away. Relatively speaking, it doesn't seem so far-fetched that the aging process could be halted, or reversed, for those beyond their prime. Still, let's not get ahead of ourselves. We must first understand the mechanisms behind aging before we tamper with them. But where to begin? How might this be accomplished? And if we could, should we meddle? Recent research into the aging process shows promise, and scientists have turned toward an uncommon disease which instigates early aging in children, hoping to learn more.

Hutchinson-Gilford Progeria Syndrome (HGPS) has been fairly well documented since the late 19th century, although little aside from its expressed symptoms was known about the disease. Giant leaps in the field of molecular and cellular genetics have allowed researchers to shine some light on the matter, as well as on the normal aging process. HGPS is extremely rare and affects merely one in four million to one in eight million born, depending on the statistical source. Nevertheless, compared to more common diseases, it receives a disproportionate amount of attention due to its peculiar symptoms. Of these, the most easily recognized is described within the Greek roots of the ailment's name: *Pro* 'early' and *geras* 'old age.' It was initially termed Progeria by Doctor Hastings Gilford, although Doctor Jonathan Hutchinson first explained the ailment in 1886 (Hennekam, 2006). Hutchinson, a famed British surgeon and expert on syphilis, originally described the aged appearance of a six-year-old boy who looked many times his age (Shah, 2007). The report was plainly titled, "A case of congenital absence of hair with atrophic condition of the skin and its appendages." Gilford described an identical case in a three-and-a-half-year-old with a misdiagnosed case of ectodermal dysplasia (which affects child tissue development) and subsequently published his own detailed study complemented with pictures in

1904 (Hennekam, 2006). As the disorder's full name indicates, the two doctors share credit in the discovery and early analysis of Hutchinson-Gilford Progeria Syndrome—more commonly abbreviated as Progeria.

Historically there have been just over 100 reported cases (Shah, 2007), and currently 42 children are afflicted (Progeria Research Foundation, 2004). Researchers speculate that more undiagnosed cases are likely to exist, which accounts for the range of occurrence from one in four to eight million. Variance within this statistic is mirrored by other demographically-based numbers, such as the incidence of males to females. Currently, the Progeria Research Foundation claims there is no bias favoring expression in either gender. This contradicts Franklin Debusk's comprehensive study in 1972 of all reported cases. He calculated predominance in males by a ratio of 1.5:1. Since his report, the figure has dropped to 1.2:1. Furthermore, of the 23 living, afflicted Europeans, 11 are males and 12 female (Hennekam, 2006). The trend lends credence to the Progeria Research Foundation's "no-preference" assertion, which may be attributed to changing times and technology, allowing for more comprehensive reporting methods and analysis.

Given these technological advances, why spend valuable time and resources researching a disease that affects just a few people and has seemingly little consequence on global health? Almost the entire human population is concerned about aging; the young worry about their looks, the middle aged about their looks and memory, and the elderly about their looks, memory, and health. A study conducted by Rebecca Yun and Margie Lachman (2006) on the perceptions of aging found that "those who were experiencing aging more directly showed the greatest amounts of fear." Yet, in Americans at least, everyone showed concern, as people of "all ages are exposed to the expected negative changes that accompany aging through common images portrayed in advertising and entertainment programs" (Yun & Lachman, 2006). Reality television programs such as *America's Next Top Model* and *Project Runway* seem to exacerbate the damaging effects of aging on one's life. While the more refined may abstain from these nonsensical shows, they certainly saw what Sir Lancelot the Brave, Sir Galahad the Pure, and Sir Robin the Not-Quite-So-Brave-as-Sir-Lancelot were willing to endure for a shot at eternal life in *Monty Python and the Holy Grail*. The multi-billion dollar cosmetics and nutritional supplement industries' income statements provide further evidence to support the assertion that an ever aging populace

is trying to stay youthful. And while we might be looking at cutting edge ways to look young and fit, it is certainly not a new trend. Even before the know-how existed, quacks and frauds prescribed "sure-thing" remedies to slow and reverse the inevitable. The 1920s advertisement in figure 1 depicts a soap that "magic[ally]" erases fat and age, allowing you to be "as slim as you wish." Maybe Adonis set too high of a standard and ruined it for the rest of us homely mortals. Instead of just being content, it is human nature to strive for betterment. These aspirations at least partially constitute one's willingness to live. Premature aging diseases provide accelerated models through which many hope to gain insight into the human aging mechanism. Natural anomalies such as HGPS essentially tweak one or a few cogs in the overall mechanism and allow us to see the end result. They provide an extremely effective model for analyzing the body's maturation process.

Figure 1. Advertisement for La-Mar Reducing Soap. Available online at <http://www.faqs.org/nutrition/images/nwaz_02_img0199.jpg>.

This research raises a number of ethical questions. Surely it is not politically correct to suggest reasons for Progeria research aside from curing the disease itself. In the same way that children today inject themselves with Human Growth Hormone so their physical stature complements their professional basketball player ambitions, will adults one day be able to match their 35-year-old mentality with a body that doesn't age beyond this benchmark? If historic and earth-shattering discoveries have taught us anything, it might be that what seems distant now could perhaps be a reality tomorrow. Luckily, because of our obsession with aging, Progeria continues to be scrutinized, and a cure may yet be found.

Progeria is sometimes inaccurately used to describe a range of early-onset aging ailments (such as Werner's syndrome, which doesn't affect pre-pubescent children). In fact, it pertains solely to Hutchinson-Gilford Progeria Syndrome. Until recently, this confusion was somewhat justifiable as there were no definitive tests for Progeria: the ailment was subjectively diagnosed provided that enough symptoms fit. Lately, advances in genetics and molecular biology have paved the way for a definitive diagnosis (Progeria Research Foundation, 2004). Yet, because of the disease's infrequent manifestation, no routine screening for Progeria exists. Accordingly, physicians continue to rely for diagnosis on the peculiar, expressed phenotypes which accompany the disease.

An individual is most often diagnosed with Hutchinson-Gilford Progeria Syndrome within the first few years of birth. Of course this varies from case to case and depends upon whether the individual exhibits classical HGPS or Non-Classical Progeria, which closely overlaps the symptoms of mandibulo-acral dysostosis (Hennekam, 2006). The Progeria Research Foundation states, "Although they are born looking healthy, children with Progeria begin to display many characteristics of accelerated aging at around 18–24 months of age." A combination of clinical indications of accelerated aging, "including loss of subcutaneous fat and muscle, skin atrophy, osteoporosis, arthritis, poor growth, and alopecia," serve as tell-tale signs of HGPS (Shah, 2007). The photographs in figure 2 illustrate how these physical abnormalities become progressively visible (Hennekam, 2006). The child appears healthy during his first year, but eyebrow, hair, and weight loss, as well as lobe-less ears, identify the disease when the child is two. At 12, a shrunken chin, scleroderma, and a beaked nose all present themselves. Raoul Hennekam's *Review of the Phenotype* notes that joint stiffness and decreased mobility, in part due to the abnormal growth of bones and arthritis, are also common. He goes on to report high-pitched voices, crowded teeth, and unusual patterns of spermatogenesis and menstruation in patients. No afflicted male is known to have fathered any children, although a woman with non-classical HGPS gave birth to a healthy child at age 23. While the clinical signs of HGPS are fairly distinct from other diseases, it does share commonalities with Mandibulo-Acral Dysostosis (MAD) and Restrictive Dermopathy (RD) which can lead to misdiagnosis. The table in figure 3 illustrates how symptoms of the three diseases compare. Surprisingly, Progeria is not accompanied by the illnesses commonly associated with old age such as

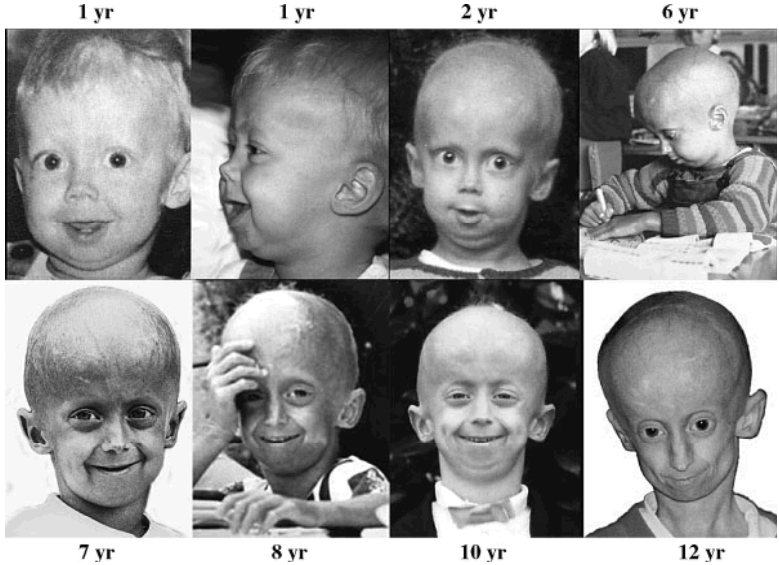

Figure 2. Dutch Patient 2 at the age of 1 year, 1 year, 2 years, 6 years, 7 years, 8 years, 10 years, and 12 years. R. C. M. Hennekam. (2006). Am J. Med. Genet. Vol. 140A, 23: 2603–24. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

senility, cancer, or reduced hearing and vision. Nonetheless, with age comes death, and physically mature Progeria patients are no exception to this rule, despite their youth. With a range of 7 to 27, the average life expectancy of a patient today is roughly 13 years (Shah, 2007). In non-classical Progeria, "growth can be less retarded, scalp hair remains present for a longer time, lipodystrophy is more slowly progressive, osteolysis is more expressed except in the face, and survival well into adulthood is not uncommon" (Hennekam, 2006). In many respects, non-classical HGPS is a subdued version of the conventional disease. Nonetheless, it eventually reaches the same grave end result. Dr. Kara N. Shah, of the Children's Hospital in Philadelphia notes, "Death due to cardiovascular abnormalities occurs in approximately 75% of patients. Other causes of death mentioned in the literature include stroke, marasmus, inanition, seizures, and accidental head trauma" (Shah, 2007). Only one case has involved malignancy. The disease itself does not directly incite death; instead, it predisposes the body to a number of other unavoidable health issues to which all Progeria patients eventually succumb.

	HGPS	MAD	RD
Pinched nose	++	+	+
Prominent vessels	+++	+	+
Lipodystrophy	+++	+	–
Clavicular hypoplasia	+	+++	+
Micrognathia	+	+++	+
Acro-osteolysis	+	+++	+
Stiff skin	+	–	+++

Figure 3. Comparison of Major Symptoms in the Three Laminopathies that Show Generalized Symptoms: Hutchinson-Gilford Progeria Syndrome (HGPS), Mandibulo-Acral dysostosis (MAD), and Restrictive Dermopathy (RD). R. C. M. Hennekam. (2006). *Am J. Med. Genet*. Vol. 140A, 23: 2603–24. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

In the past medical science could provide little hope for diagnosed patients, and even today no cure exists. However, technological advances in genetic and cellular processes have exposed the blueprints of the disease. In October of 2003, the Progeria Research Foundation announced the detection of a mutation believed responsible for the disease. The LMNA gene codes for the Lamin A protein, which in turn provides structural integrity to a cell's nucleus. Paola Scaffidi and Tom Misteli recently published a paper in the journal *Science* which contends that a sporadic autosomal dominant mutation of this gene causes aberrant splicing and a defunct protein called Delta 50 Lamin A (indicative of a 50 amino acid deletion). Because the mutation is random, this finding bolsters the most recent claims that Progeria has no gender bias. However, Hennekam (2006) suggests that non-classical HGPS is probably an "autosomal recessively inherited disorder, either because of parental consanguinity or because of recurrence in siblings." In either case, the LMNA alteration results in "dysmorphic nuclear shape," "increased DNA damage," "down-regulation of several nuclear proteins," and "altered histone modification patterns" (Scaffidi & Misteli, 2006). It didn't take long for researchers to recognize that the cells in healthy elderly individuals, those not afflicted by HGPS, display similar characteristics. Following the next logical step, the researchers tested and confirmed Delta 50 Lamin A's presence in the naturally aging population. Scaffidi & Misteli also note that the presence of the mutant, both in the elderly and in individuals with HGPS, causes Lamin A to congregate at the periphery of the nucleus, whereas young, non-afflicted individuals express elevated levels of the wild-type

protein in the nucleoplasm. These similarities between the healthy old and Progeria patients intimate a correlation between the mechanisms induced by HGPS and those of normal physiological aging. Additional studies will likely improve our understanding of aging as well as provide a means to treat Progeria.

As it stands, Progeria is cared for symptomatically; as a problem presents itself, a treatment is suggested. Shah (2007) suggests that the Hutchinson-Gilford Progeria Syndrome demands the attention of several specialists in a system of coordinated care. Pediatric cardiologists, physical and occupational therapists, dermatologists, gastroenterologists, and dentists are all essential to treat the many aforementioned symptoms. However, now that the responsible gene aberration has been identified, a number of theoretical and highly experimental treatments are in the works. These options include "the use of viral vectors to deliver antisense molecules to blood vessels such as the aorta and coronary arteries, the sites where they are needed most," "selective inhibition through small molecules (or other RNA interference techniques) of the alternative splicing caused by the classical mutation," and "inhibition of farnesylation (post-translational modification of a protein) of pre-lamin A, which was shown to restore the nuclear envelope phenotype in vitro" (Hennekam, 2006). Whether or not any of these remedies will be effective in treating Hutchinson-Gilford Progeria Syndrome patients or the elderly who express mutant Lamin A remains unknown. It can only be assumed that more potential therapies will arise as our understanding of science and genetics develops, but for the ailing and aging alike, it remains a race against time.

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