SCID’s Kids

Genetics and Human affairs: Severe Combined Immunodeficiency

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“I have neither given nor received unauthorized aid on this assignment.”
Introduction:

A cough, a sneeze, a dirty hand rail are everyday encounters, that at worst leave most people a little grossed out, but for a select group of children these simple actions could mean death. These children are affected by Severe Combined Immunodeficiency Disease (SCID). SCID has also been dubbed the bubble boy disease due to early treatment practices for the disease. With proper screening for the disease, SCID can be detected early and treated through either gene therapy or bone marrow transplants. Great strides have been made in treatment of this disease since the days of placing children in a “bubble” or germ free environment. In recent decades the proverbial light at the end of the tunnel for SCID’s kids is becoming more and more of a reality with each passing day. “Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients survive” (Diseases of the Immune System, p. 10).

Part A:

“SCID is a group of very rare-and potentially fatal-inherited disorders related to the immune system” (www.learn.genetics.utah.edu). In the typical child the immune system is utilized to fight off attacks from dangerous bacteria and other harmful agents. Infants born with SCID have a glitch in their immune system, which leaves them with little or no protection from potentially deadly infections. “The defining feature of SCID…is a defect in the specialized white blood cells (B- and T-lymphocytes) that defend us from infections by viruses, bacteria, and fungi” (Diseases of the Immune System, p. 10).

Although there is not a central database specifically stating exactly how many babies are diagnosed with SCID each year in the United States, it is estimated that the
number falls somewhere between 40-100. In addition, researchers have no way of knowing how many undiagnosed infants die of SCID each year (http://genome.gov/13014325). Often time children with SCID are either misdiagnosed or not diagnosed until it is too late. The classic characteristics of SCID are an extreme susceptibility to infections of the ear, pneumonia or bronchitis, oral thrush and diarrhea—none of which are typically life threatening. It is recommended for young infants who show persistent infections or various levels of impairment that parents seek testing for SCID and other possible immune deficiency diseases. As a result of this continued assault on their small bodies, most of these children suffer from a failure to thrive. If SCID goes untreated, affected children can not expect to live past the age of two.

All forms of SCID are inherited. “The most common type of SCID is called XSCID because the mutated gene, which normally produces a receptor for activation signals on immune cells, is located on the X chromosome. Another form of SCID is caused by a deficiency of the enzyme adenosine deaminase (ADA), normally produced by a gene on chromosome 20” (www.genome.gov/13014325).

X-linked SCID is found almost exclusively in males. “X-linked SCID is the most common form of severe combined immunodeficiency. The exact incidence is unknown, but the condition probably affects at least 1 in 50,000 to 100,000 births” (http://www.ghr.nlm.nih.gov/condition=xlinkedseverecombinedimmunodeficiency). The gene affected in X-linked SCID is a mutation in the interleukin 2 receptor, gamma or IL2RG. This gene is responsible for providing instructions for the making of a protein that is essential to the proper function of the immune system. The protein that is made is crucial for the development and growth of the developing immune system cells called
lymphocytes. “Lymphocytes defend the body against potentially harmful invaders, make antibodies, and help regulate the entire immune system” (www.ghr.nlm.nih.gov). The faulty piece of the lymphocyte receptor is named the “common” gamma chain, “because it is a common component of lymphocyte receptors for several types of cytokines, including the interleukin-2 (IL-2) receptor” (http://genome.gov/13014325). Without properly functioning lymphocytes, the body is unable to ward off infections. As mentioned above X-linked SCID occurs almost exclusively in males. This happens because females have two X chromosomes. If one of the females IL2RG gene’s development is interrupted by a mutation, they still have the other normal gene on the second X chromosome; thus, allowing them to enjoy normal immune system function. Males, however, do not have this same back up gene. Therefore, a mutation in the IL2RG gene causes males to produce immune cells that do not function properly. As a result of XSCID being the most common form of SCID, the incidence of SCID is much higher in the male population than in the female population.

Another heavily researched form of SCID is Adenosine Deaminase Deficiency SCID, commonly referred to as ADA SCID. This form of SCID is an extremely rare genetic disorder. ADA SCID is a “systemic purine metabolic disorder that primarily affects lymphocyte development and function….Infants with ADA-deficient SCID have failure to thrive and opportunistic infections associated with marked lymphocytopenia and the absence of both humoral and cellular immune function” (Hershfield, 2006, p.1). ADA SCID is extremely rare and is estimated to occur in only 1 in 200,000 to 1,000,000 newborns worldwide. It is only responsible for about 15% of all SCID cases. Most individuals with ADA SCID are diagnosed with this disorder within the first six months
of their lives. There are approximately 10-15% of cases which are termed “delayed onset” because they do not appear until 6 to 24 months of age or even as late as adulthood which is termed “late onset”. The late onset group tends to be much less severe, causing mostly recurrent upper respiratory infections and ear infections. The ADA gene’s primary function is to provide instructions for producing the enzyme adenosine deaminase. “This enzyme is found throughout the body but is most active in lymphocytes, the specialized white blood cells that protect the body against potentially harmful invaders by making antibodies or by directly attacking virus-infected cells” (http://www.ghr.nlm.nih.gov/condition=adenosinedeaminasedeficiency). The main function of the adenosine deaminase enzyme is to remove a molecule called deoxyadenosine that is generated during the denaturing of DNA. “Adenosine deaminase converts deoxyadenosine, which is toxic to lymphocytes, to another molecule called deoxynosine that is not harmful” (http://www.ghr.nlm.nih.gov/condition=adenosinedeaminasedeficiency). The ADA form of SCID is inherited via an autosomal recessive pattern.

In the past, effective treatment of SCID was seen as literally a sterile bubble. Now there are different and much more effective treatments available to those who suffer from this disease. The most reliable treatment is a transplant of stem cells from the bone marrow of a healthy person. The greatest chance for curing SCID comes from a bone marrow transplant from the tissue match of a sibling. Also the transplants that are performed in the first three months of life tend to have the highest success rate. Unfortunately, bone marrow transplants are not 100% accurate or effective. This realization lead researchers to explore other potential treatment options; thus, gene therapy was born. In 1990, the first gene therapy experiments on humans were conducted.
“Two girls with ADA deficiency SCID were treated, several times, over a 2 year period, with T-cells carrying corrected DNA” (http://www.scid.net/about.htm). The researchers took a sample of the girls' defective T-cells, corrected them and then returned these T-cells to them. The success of this trial is debated, the girls still receive replacement enzyme therapy; thus, this experiment was not completely successful, but it does give hope that if enough cells in the patient are corrected then the disease can be corrected. In early 2000, two cases of X-linked SCID were treated by gene therapy. These two patients had no prior treatment of any kind. When these patients were evaluated at 10 and 11 months after therapy they were both demonstrating normal growth and development without any additional treatments. This trial published in Science Magazine in April of 2000 had ten XSCID patients treated. However, when another article was published in Science Magazine in October 2003, it was revealed that two of the boys treated developed a T-cell problem similar to leukemia. Once this news reached the world, gene therapy trials on XSCID were largely placed on hold. As of 2006 new trial have been started that exhibit extreme caution, when inserting the corrected DNA. In reality gene therapy is still the most promising hope to truly curing this debilitating disease. (http://www.scid.net/about.htm).

Part B:

Imagine living in a clear, sterile room that measures six feet by two feet by four and a half feet and is housed inside the Texas Children’s Hospital. Leaving this room would mean almost certain death for its occupant. Add to the equation that you are just a child who has never experienced the outside world. Is this any kind of life? Can this even be considered a humane existence? For a child named David, this was the only life he
ever knew. David Vetter is probably the most well known victim of Severe Combined Immunodeficiency. He was born on September 21, 1971 and died on February 22, 1984. The obvious question becomes: How did he survive for twelve years with SCID? Keep in mind; this is before the development of very successful bone marrow transplants or gene therapy. The answer seems almost eerily simple- 10 seconds after his birth he was placed in a completely sterile plastic isolator which would become his home and with time would grow as he did. The Vetter’s had given birth to another son a year earlier, who died from XSCID; thus, allowing them to prepare for the birth of their second son, David. The plan to place the second son in a bubble was put in motion before he was even conceived. Doctor’s convinced the parents that a cure for SCID was not far in the future and that the newborn could be placed in a sterile isolator until that cure was found. In the beginning of this process, the ethicality of the project was not spoken of everyone hoped that a cure would come soon. (McVicker, 1997, p. 1).

David was eventually moved to a room at the Texas Children’s Hospital, where his bubble was enlarged to include a “crib bubble” and a “supply bubble,” which was well stocked with sanitized items like diapers, clothes, vitamins, food, medicine and water. The walls of the bubble had reinforced rubber gloves, so that David could be cared for by others. In many ways David became a tourist attraction of sorts, he was visited by royalty and celebrities. By the time he was three years old and the possibility of leaving the bubble was nowhere in sight, David was allowed to go home for short periods of time, (where another bubble was set up). In 1974 psychologists became interested in David’s development, considering his very unique environment, psychological testing began. Around this same time, after David had been in his bubble
for three and a half years, the ethicality of what was happening to him was discussed by a formal gathering of doctors at the hospital. The most poignant moral issue was brought up after this meeting, when the Reverend Raymond J. Lawrence (chaplain of Texas Children’s hospital) commented “The great scandal of the Bubble Boy was that he was conceived for the bubble…The team that did this didn’t think through this very well. They didn’t consider what would happen if they didn’t find an immediate cure. They operated on the assumption that you could live to be 80 years old in a bubble, and that would be unfortunate but okay.” No conference was ever established to examine this claim, although it is speculated that several hospital staffers, who worked closely with David, felt the same way. The doctors who originally presided over David’s case denied this claim and eventually moved on to other projects. A lady named Mary Murphy, a physiologist working with David, became a close friend and confident. She wrote about how his limited life in a bubble was affecting him psychologically. He developed a deep fear of abandonment, and as he got older he began to fear going insane. He also developed several facial tics and was plagued by dreams of germs coming to kill him. According to Murphy, David asked her “Why didn’t they do something to me before I was old enough to care. When I was three, I wouldn’t have cared. When all this mess started, didn’t they ever think about or realize that they were dealing with my life? They made decisions without ever thinking about anything except what they wanted to do, not about all this crap that I’m in.”

Eventually in 1980 one of David’s doctors admitted that a cure for David was still years away and federal funding for the project would eventually dry up. Overall the costs to keep David alive for his short, restricted twelve years hit somewhere around 1.3
million dollars. The doctors suggested that the Vetters remove David from the bubble and place him on an aggressive regime of gamma globulin and antibiotics. In reality this would be away to bring David out of the bubble with little hope for survival, with this in mind the Vetters rejected this idea. Almost four years later it was decided that something had to be done, David could not be the bubble boy forever. At this same time doctors in Boston had made some advances in transplanting bone marrow that was not a 100% match. His only hope was a partial-match bone marrow transplant from his older sister. Just after his 12th birthday the transplant was completed. Initially, for a few months after the transplant everything seemed to be going well. Suddenly, he became plagued with diarrhea, fever and vomiting. This tragic turn of events resulted in his removal from the bubble and eventual death 15 days later. “It turned out that the screens of (his sister’s) bone marrow had missed the presence of Epstein-Barr, the virus that produces mononucleosis. An autopsy revealed that David’s body was riddled with tumors; he died of Burkitt’s lymphoma” (McVicker, 1997, p. 4). As mentioned above, the genes for XSCID and lymphocytes are directly tied to the function of the immune system; therefore, it is no surprise that David developed a disease that affects the lymphocytes. The most positive aspect to come out of the Bubble Boy story is that David’s autopsy showed doctors everywhere that cancer can develop from viruses. (McVicker, 1997, p. 1-5)

The consequences a story like David’s holds are far reaching both from an ethical and a medical perspective. In my opinion the entire “experiment” was unethical from the beginning. Giving parents hope that their child could be left in a sterile environment and then be given a cure is ridiculous. Dooming a child to a life in a bubble is immoral, this
should have never happened intentionally. David’s life was one of great torment and fear. The simple pleasures that I enjoy everyday; a walk in the sun, a hug from my parents, the feel of a spring rain shower, he never knew. That isn’t a life, it is a science experiment. The emotional and developmental trauma that David must have experienced is unfathomable.

Fortunately with the advancements of medical science, the survival rate for children who suffer from SCID has risen. What used to be a death sentence, now offers hope. According to Buckley et. al. “infants who received transplants before 28 days, developed higher T lymphocyte counts and higher lymphocyte responses to mitogens than did infants who were transplanted after the immediate neonatal period of 28 days. Importantly, survival of those patients transplanted in the first 28 days of life was 95% (versus 74% in the >28 day group).” This is a very exciting possibility considering that David was doomed to a life in a bubble. In addition to the bone marrow transplants, screening of newborns ensures early detection which could further increase the 95% survival rate. The National Institutes of Health released an article in 2005 that stated “The newly developed screening tool exploits a detailed understanding of the maturation of T cells…Using a quantitative laboratory technique that measures the number of these rings within a blood sample, Dr. Puck’s group was able to differentiate normal infants from those with SCID. In dried blood samples from healthy babies, the team was able to detect an average of 1,000 of these genetic rings; children with SCID had 30 or fewer.” The future of SCID seems very bright. It is no longer seen as an almost certain death sentence when a baby is born with SCID.
With the unraveling of the Human Genome Project came an entirely new branch of medical research known as gene therapy. This development opened up a line of treatment for children suffering from SCID. In 2002 the most extraordinary procedure, which moved the world one step closer to a complete cure for SCID, was carried out. Rhys Evans from the United Kingdom was successfully treated with gene therapy. No matching bone marrow donor could be found. Therefore, a team of doctors at London’s Great Ormond Street Hospital, led by Dr. Adrian Thrasher, took bone marrow from Rhys, and then utilized a virus to move a new and healthy version of the gene into his nonfunctioning immune cells. “This was then reimplanted into the patient, where it gradually began to generate further cells to pass into the bloodstream and protect him from infection. Now he has a normal count of immune cells for a child of his age, and doctors are hopeful this will continue.” (http://news.bbc.co.uk/2/hi/health/1906999.stm) Rhys mother was quoted as saying “after his gene therapy, he was running around at home-he’s a normal little boy now.” Reading these words proves that there are great mysteries of science that are yet to be solved and with the presences of modern day technologies they are becoming a reality.

The public was first captivated by SCID when they saw photos of the young David Vetter in his bubble. Now there are numerous foundations set up to support children and families that are affected by Severe Combined Immunodeficiency Disease. Each year at the Texas Children’s Hospital a one mile run is sponsored in David’s name to raise both money and awareness for others suffering from life threatening diseases of the immune system. In the years since the Bubble Boy, both scientifically and ethically, researchers have made tremendous advancements in the treatment and curing of SCID. I
feel as though the tragic story of David and his struggle to survive brought to light the simple truth that not everything is just in the name of science.
References:

Introduction:


Part A:


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**Part B:**


Additional interventions for SCID and non-SCID T-cell lymphopenia included immunoglobulin infusions, preventive antibiotics, and avoidance of live vaccines. Va. @article{Kwan2014NewbornSF, title={Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States.}, author={Antonia Kwan and Roshini S. Abraham and Robert J Currier and Amy M. Brower and Karen Andruszewski and Jordan K Abbott and Mei W Baker and Mark Ballow and Louis E. Bartoshesky and Francisco A. B. Bonilla and Charles D. Brokopp. Severe Combined immunodeficiency syndrome (SCID) is a rare and serious type of inherited immune deficiency resulting in poor function of the immune system. A SCID diagnosis is a medical emergency which requires early treatment. This article aims to increase awareness, enabling early diagnosis and specialist referral for potentially lifesaving treatment. Incidence of SCID is estimated to be approximately 2:100,000 live births a year (1,2). It is caused by genetic defects that affect the function of T cells, B cells and/or Natural Killer (NK) cells (depending on the type of SCID). SCID leads to Severe Combined Immune Deficiency (SCID, pronounced "skid") is a potentially fatal primary immunodeficiency in which there is combined absence of T-lymphocyte and B-lymphocyte function. There are at least 13 different genetic defects that can cause SCID. These defects lead to extreme susceptibility to very serious infections. This condition is generally considered to be the. Severe Combined Immune Deficiency (SCID, pronounced "skid") is a potentially fatal primary immunodeficiency in which there is combined absence of T-lymphocyte and B-lymphocyte function. There are at least 13 different genetic defects that can cause SCID. These defects lead to extreme susceptibility to very serious infections. Severe combined immunodeficiency-X1 (SCID-X1) is an X-linked inherited disorder characterized by an early block in T and natural killer (NK) lymphocyte differentiation. This block is caused by mutations of the gene encoding the γc cytokine receptor subunit of interleukin-2, -4, -7, -9, and -15 receptors, which participates in the delivery of growth, survival, and differentiation signals to early lymphoid progenitors. After preclinical studies, a gene therapy trial for SCID-X1 was initiated, based on the use of complementary DNA containing a defective γc Moloney retrovirus-derived vector and ex Severe Combined Immunodeficiency (SCID) may be best known from news stories and a movie in the 1980s about David, the Boy in the Bubble, who was born without a working immune system. Caused by defects in any of several possible genes, SCID makes those affected highly susceptible to life-threatening infections by viruses, bacteria and fungi. Because David's brother had died of the disease, doctors immediately placed him into a plastic isolation unit to protect him from infections. He lived in such isolators for nearly 13 years. David died in 1984 following an unsuccessful bone marrow trans