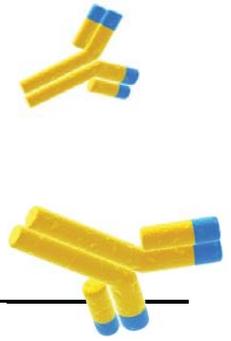
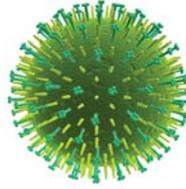


# Immunological Malfunction?

by

Karen A. Pinco  
Department of Biology  
Westfield State College, MA



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## ***Immunoglobulins***

Susan and Joe were worried. Their little boy, Daniel, had been having an awful lot of bacterial infections and he was barely a year old. It seemed that the antibiotics cleared up one bacterial respiratory infection only to have another follow shortly. The scary thing was that Daniel had just fought off a case of pneumonia caused by *Pneumocystis carinii*, a fungal infection that was usually found in people with HIV. Waiting for the test results of an HIV test for their little boy was one of the worst waits ever. Thank goodness it came back negative.

However, it seemed that their troubles were just beginning. After this last lung infection, the fungal one, and a negative HIV test, their doctor had ordered a number of other blood tests, including a genetic test that Susan didn't fully understand. Apparently the doctor was worried about Daniel's immune system functions. Susan had also met with a genetic counselor who collected a family history of any immune disorders. The details were vague, but Susan's mother, Helen, knew that one of her three brothers had died young from an unexplained lung infection. Unfortunately, Grandma Ruth had passed away a few years ago, leaving them with numerous unanswered questions.

Susan and Joe had an appointment with their doctor that afternoon to go over the results. When they arrived Dr. Dresdner led them into an office where Ms. Henchey, the genetic counselor, waited. This can't be good, thought Susan. The doctor began by explaining that they had analyzed Daniel's blood and found that while he had normal levels of B cells and T cells, his antibody levels were anything but normal. The levels of IgG, IgA, and IgE were very low, almost undetectable, and Daniel had abnormally high levels of IgM and IgD. He went on to explain the nature of these different categories of immunoglobulins.

1. List the different immunoglobulin types and explain where they are found and what their functions are.
2. Looking over this list, do Daniel's recurrent lung infections make sense? Why?

## ***Isotype switching***

The doctor went on to explain that IgM was the first kind of antibody made by B cells in response to the appearance of an antigen, and that Daniel appeared to be making these immunoglobulins just fine. However, it appeared his immune system failed to undergo immunoglobulin isotype switching. Susan and Joe were confused and had several questions.

3. What is an antigen?
4. What is immunoglobulin isotype switching?
5. How does the failure of immunological isotype switching explain the lack of IgG, IgA, and IgE in Daniel's blood?
6. Is this the only explanation for the lack of IgG, IgA, and IgE in Daniel's blood?
7. Why do you think the doctor suspected the need for genetic testing?
8. What is the role of a genetic counselor?

## ***Pedigree***

After answering Susan and Joe's questions, the doctor asked Ms. Henchey to present her analysis. Ms. Henchey presented them with what she called a pedigree, a kind of family tree with circles and squares, which indicated that her little boy and her mother's brother had something in common. The counselor stated that the results of DNA analysis showed that Daniel had X-linked agammaglobulinemia with hyper-IgM syndrome. She then showed Susan and Joe how this syndrome had most likely been passed down through the family tree. Ms. Henchey also suggested that Susan's two younger sisters consider being tested for this syndrome.

9. Draw out the family pedigree that the counselor is presenting and show how this X-linked genetic disorder has passed through Susan's family tree.
10. Why is the genetic counselor suggesting genetic testing for Susan's sisters?

## ***CD40***

The counselor then went on to explain that there was a genetic mutation in the gene for the CD40 ligand. This ligand is found on activated T cells and is responsible for binding to the CD40 receptor on B cells. The mutation prevented it from functioning correctly.

11. Which cells have the CD40 ligand? Which cells have the CD40 receptor? What does their interaction cause? How does this explain Daniel's immunological deficiency?

## ***Treatment or cure?***

The doctor took over again. Dr. Dresdner explained that there was treatment for this disease. Daniel would need immunoglobulin infusions every three to four weeks in order to provide him with missing IgG and hopefully lower the abnormally high level of IgM in his bloodstream. Also, although current therapies could result in a happy, healthy adult, Daniel was at risk for an increased rate of liver disease. However, the doctor stated, there was a potential cure. A bone marrow transplant or cord blood stem cell transplantation, particularly from a matching HLA sibling, could provide a permanent cure. Someday, the doctor stated, gene therapy may be an option, but not at the present moment.

12. What is immunoglobulin therapy? Why will Daniel need a transfusion every three to four weeks? Why do you think it will lower his IgM levels?
13. How can a bone marrow or cord blood stem cell transplant cure Daniel?
14. What is HLA? Why is a matched sibling the best possible donor?

## ***Home again***

Relieved that their little boy had treatment options, but concerned that there would be more infections and possibly liver disease, Susan and Joe decided that they would start working on expanding their family sooner, rather than later. However, they had difficult decisions ahead. Should they undergo prenatal testing? Should they attempt to guarantee Daniel a sibling with matching HLA?

15. What is prenatal testing?
16. How would Susan and Joe be able to select a child with matching HLA?

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