This chapter provides answers to these questions:

- Will there always be new people in the world with hemophilia?
- Will hemophilia be treated more effectively and safely in the future?
- Will the treatment of hemophilia always involve injections?
- Can hemophilia be cured?
- If gene therapy is to be used to treat hemophilia, how will it be performed?
Will there always be new people in the world with hemophilia?

The number of new cases of hemophilia in the world will likely remain constant over the coming years. The reason is this.

Hemophilia is a disease that results from changes to the genetic code for a clotting factor. In many cases it is possible to trace a family history of hemophilia. However, in about one-third of new patients, hemophilia appears to occur in that family for the first time. This is called a sporadic or isolated case of hemophilia. There is now good evidence to indicate that these cases of hemophilia are due to new changes in the human genetic code. Changes to the genetic code happen in all of us, all of the time. In most instances, the body has ways to detect and repair these changes, but sometimes the new genetic changes remain. Many of these changes go unnoticed, having no effect on the way in which the body looks or works. However, the genetic change affects a region of code that controls the ways in which certain clotting factors are made. A new case of hemophilia is created. Hemophilia A (factor VIII deficiency) is more common, at least in part because the factor VIII gene is much bigger and thus more error-prone than the factor IX gene.

There is no reason to believe that this new rate of “hemophilia creation” will change in our lifetimes; in fact, the human genetic code has probably been changing at the same rate for millions of years. With new cases of hemophilia appearing at the same rate and people with hemophilia living longer, the total number of people with hemophilia in the population will very likely increase in the next decade.
Will hemophilia be treated more effectively and safely in the future?

It is very important to realize that the current treatments for hemophilia are both very effective and very safe. Certainly, the progress that has been made in treating this disease over the past 50 years has been dramatic.

Nevertheless, there is little doubt that scientists will continue to search for even better forms of treatment.

The first area for future progress is in new forms of the recombinant clotting factors, proteins made using DNA biotechnology. There are already studies showing that the normal clotting factors can be changed in subtle (or not so subtle) ways to make the proteins better for hemophilia treatment. This is called clotting factor modification. These modifications can take different forms.

- Xyntha®, one of the recombinant forms of factor VIII currently in use, is missing the middle part of the factor VIII molecule. This modification means that the protein is smaller and easier to make, but it doesn’t interfere with the way the protein works to stop bleeding.

- A second example of clotting factor modification is a new factor VIII protein with a longer half-life. In other words, it is better at resisting elimination from the bloodstream. This type of protein will circulate in the blood for a longer period and may result in a reduction in the frequency of factor VIII infusions. There are various ways in which this result can be achieved and the first of these modified, longer-lasting factors is beginning clinical trials.

- A third example is a form of factor VIII that is less likely to spark a response from the immune system. This new factor VIII may result in a reduced risk of inhibitor development, one of the most serious complications in the treatment of hemophilia.
These and other modifications to the normal clotting proteins require long study in the research laboratory. The proteins are tested with hemophilic mice and dogs before they enter human clinical trials.

When thinking of improving clotting factor safety, it is essential to keep in mind the fact that the current recombinant factors are already very, very safe. Recombinant factors have never been known to transmit disease. To prove that any new treatment is safer than the current therapies would take a trial in thousands of patients over many years. Nevertheless, despite the current very high level of safety, research is still being carried out to develop clotting products that are even safer — although this will always be a theoretical improvement, as opposed to one that is clinically proven.

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Did you know...

that Elisa, a Beagle cross, living in Kingston, is one of many hemophiliac dogs from an extended family that have made invaluable contributions to hemophilia research?

- Will the treatment of hemophilia always involve injections?

The clotting factors that are missing from the blood of people with hemophilia are relatively fragile proteins that do not survive for long outside of the bloodstream. This is why current therapy involves direct injection of the clotting factors into the blood.

However, alternative routes for delivery of the clotting factors are under investigation. These include the possibility of inhaling the factors in the same way that people with asthma treat themselves with “puffers.” With this type of delivery, the inhaled protein is absorbed rapidly into the bloodstream from the small blood vessels inside the lungs.

The other route of delivery that continues to attract attention involves taking the factor by mouth in the form of a tablet or syrup. Here, the problem of getting the factors through the stomach and upper intestine without damage to the clotting activity is a huge challenge.
In summary, although alternative routes to administer clotting factors are still under investigation, it is very unlikely that any of these alternatives will reach patients in the near future.

**Can hemophilia be cured?**

Since the first development of *gene therapy* methods in the early 1990s, hemophilia has been a leading candidate for the application of this new type of treatment. Successful, long-term gene therapy would cure hemophilia.

The idea behind gene therapy is very simple. In hemophilia, a clotting factor gene is abnormal. The objective of hemophilia gene therapy is to deliver a normal copy of the clotting factor gene to the patient’s cells. In practice, unfortunately, the process is very complicated.

Nevertheless, by 2009, six human clinical trials of hemophilia gene therapy had already been completed. All of these trials were designed to test safety, not effectiveness. All of the trials were completed without significant side effects. Five of the trials involved the use of “paralyzed” viruses to deliver normal clotting factor genes. Three studies have involved factor VIII; the other three, factor IX. The sixth study delivered the normal genes to the patient’s cells outside of the body by shocking the cells with electricity. Once treated this way, the cells, now containing copies of the normal clotting factor gene, were returned to the patient’s abdomen to grow.

The successful completion of six safety trials tells us that effective gene therapy for hemophilia may be in the clinic within the next decade. This is more likely to be the case for factor IX gene therapy to treat hemophilia B because the size of the factor IX gene and other considerations make progress easier.

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**Did you know that...**

there is a "cure" for hemophilia? It is a liver transplant. Within hours of a liver transplant, the factor VIII or IX level of a person with hemophilia rises to normal. This is because factor VIII and IX are produced in the liver. As a result, transplantation with a normal liver constitutes a "cure".

A number of people with hemophilia have successfully undergone the procedure, not to cure hemophilia but rather because their own livers were failing. Transplantation is unlikely to ever be used to cure hemophilia. The operation is major and anti-rejection drugs are needed for the rest of the person’s life. Moreover, liver transplants are reserved for those who might die without them.
If gene therapy is to be used to treat hemophilia, how will it be performed?

This is currently a very difficult question to answer because there are several different gene therapy strategies being explored, all of which have potential for success.

The initial form of gene therapy might well involve the injection of a “paralyzed” virus that will carry the normal clotting factor gene to the cells of the person with hemophilia. Altered viruses have been used to deliver genes into the cells of animals and humans for a number of years. Researchers have developed extremely effective ways of achieving this goal. Prior to injection, the viruses are altered in the laboratory to prevent them from multiplying and causing harm once they get into the body. However, these alterations do not interfere with the virus’s ability to act as an efficient delivery vehicle for the gene.

Where and how the virus gets injected to produce the best gene therapy results is still not clear. In studies that have been performed so far, injections into muscles and into the bloodstream have both shown promise. Once delivered into the cells of the person with hemophilia, the virus takes the normal clotting factor gene to the cell nucleus where it can begin to direct the production of the normal protein.

There are now growing numbers of hemophilic mice and dogs that have had their bleeding problems successfully treated with gene therapy for periods of up to six years. The challenge is now to convert these very encouraging “pre-clinical” results to effective use in humans.
Gene therapy will not make the blood of a person with hemophilia completely normal, at least not in the near future. The hope is that the factor levels can be raised from less than 1 percent to a level between 2 and 5 percent. In other words, a person with severe hemophilia would then have moderate hemophilia. Infusions of factor concentrates would still be needed for serious bleeds and surgery.

This area of research continues to advance and it is impossible to predict how long it will take before even better therapies are developed. In theory, gene therapy should result in a long-term cure of the disease.

Conclusion

The diagnosis and treatment of hemophilia has benefited enormously from advances in medical science over the past five decades. Now, in the new millennium, with even more rapid progress in the fields of biotechnology and genetics, we can realistically look forward to a long-term cure for hemophilia.