Reading questions

1. What was causing phocomelia in children born in Europe in the '50s and '60s?
2. What were the effects of thalidomide? What percentage of children born with side effects from thalidomide survived their first birthday?
3. What were the long-term effects of these birth defects?
4. What uses has thalidomide been approved for since being initially taken off the market?
5. What are metabolites? How do metabolites complicate determining how thalidomide affects limb development?
6. Summarize the results of the CPS49 study. How does CPS49 affect limb development?
7. Summarize the experiments using cereblon. Why were zebrafish used as a model organism in this study?
8. When the gene for cereblon is altered, what effect does this have on thalidomide's ability to bind to it? What effect does this have on limb development?
9. Thalidomide was introduced to the market without its effect on pregnant women being fully tested. Many drug trials exclude women, particularly pregnant women. How would you recommend drugs be tested to ensue their safety and efficacy on the market?
10. If you're interested in the policy surrounding thalidomide and its current uses in medicine, the New York Times has a 12-minute video found here on why thalidomide was not available in the US and how its currently used in medicine: http://www.nytimes.com/2013/09/23/booming/the-death-and-afterlife-of-thalidomide.html

March 15, 2010
Answers Begin to Emerge on How Thalidomide Caused Defects
By CARL ZIMMER

The word "phocomelia" means seal limb. It describes an extremely rare condition in which babies are born with limbs that look like flippers. The long bones of the arms fail to develop, but fingers sometimes sprout from the shoulders. In some cases, the legs fail to develop, too. The French anatomist Étienne Geoffroy Saint-Hilaire coined the word in 1836, and it immediately sank into scientific obscurity for 120 years. And then, 50 years ago, it suddenly became all too familiar.

Doctors began to see more and more cases. It turned out that a drug called thalidomide, which pregnant women were taking for morning sickness, was responsible. Magazines and newspapers ran shocking pictures of seal-limbed children, and the drug was banned in 1962. By then, 10,000 children, mostly in Europe, had been born with thalidomide-induced birth defects.

Despite the notoriety, phocomelia remained scientifically mysterious for the next five decades. Doctors knew all too well to avoid thalidomide, but developmental biologists could not explain how thalidomide made limbs disappear. Only now are scientists finally starting to solve the puzzle. And by deciphering thalidomide's effects, they are discovering surprising clues about how normal limbs develop. They hope that those fundamental insights will in turn produce a medical benefit.

Thalidomide may be dangerous to developing embryos, but it is very effective for treating diseases like leprosy and some kinds of cancer. By understanding how thalidomide causes limb deformities, scientists may be able to invent safer variations of the drug. Neil Vargesson, a developmental biologist at the University of Aberdeen, in Scotland, said that like everyone, he was horrified at children being born with drug-caused defects. “If I can stop that,” he said, “that will be fantastic.”

When thalidomide first went on the market in 1957, in Germany, it was considered so safe that it was sold over the counter. Drug companies introduced it in 45 other countries. But within a few years, doctors in Germany and Australia noticed a rise in phocomelia and eventually linked it to thalidomide. In the United States, about 40 children were born with thalidomide-induced defects. When its side effects came to light, it had not yet been approved by the Food and Drug Administration.

About 40 percent of babies with thalidomide-induced defects died before their first birthday. Those who survived learned to cope. Survivors who had legs, for example, learned how to use them to dress and feed themselves. “They can do things that ballerinas can only dream of,” said Martin W. Johnson, the director of the Thalidomide Trust, which was established to assist Britain’s thalidomide survivors. Unfortunately, as the survivors enter their 50s, the strain they have put on their muscles is taking its toll. “Approximately 50 percent of our people are living with chronic pain every day,” Dr. Johnson said in an interview.

Despite the devastation, thalidomide is still in use today. In 1964, Israeli scientists discovered it could control leprosy by reducing the inflammation caused by the disease. In 1998, the F.D.A. approved it for multiple myeloma, a cancer of plasma cells in the blood. Researchers are testing thalidomide in trials for other diseases including HIV and Crohn’s disease. Patients are required to take thalidomide under strict supervision. But in South America and Africa, some women taking it are still giving birth to children with phocomelia.

How thalidomide deforms limbs has continued to baffle scientists. In the 1960s, developmental biologists began to inject thalidomide into animal embryos to trigger phocomelia. From those experiments, they developed about 30 theories. Some scientists argued that thalidomide damaged nerves in developing limbs. Others said that the drug triggered cells in the developing limb to commit suicide. And some said that thalidomide slipped into the DNA of cells in a developing limb, preventing the cells from making the proteins they needed.

Unfortunately, the scientists could not put any of those ideas to rigorous tests. They had only a crude understanding of how limbs developed, because they did not know how to track the molecular changes taking place. And so they had no way of knowing how thalidomide disrupted this chemistry.

Thalidomide itself made the puzzle even harder. When a person ingests a thalidomide pill, enzymes start to break it down into simpler forms, called metabolites. Thalidomide can

break down into at least 18 metabolites. Each one has a different structure, and, as a result, it may interact with cells in a different way. The complexity of thalidomide and the obscurity of limb formation left scientists stymied. “It went very quiet,” said Dr. Vargesson. “But all of a sudden in the past few years, it’s moved forward at a massive rate.”

In 2006, he and a team of collaborators began a survey of the metabolites of thalidomide. William D. Figg of the National Cancer Institute purified them, and Dr. Vargesson and his colleagues tested them in chick embryos. As they described in a report last year, they found that only one metabolite they tested, known as CPS49, caused the chicks to fail to develop wings.

The scientists also noticed something else about CPS49: within minutes of being injected into an embryo, it started killing developing blood vessels. Dr. Vargesson and his colleagues proposed that the death of these new blood vessels stopped the limb bud from taking its final shape.

In a healthy embryo, patches of cells along its sides swell into buds that stretch out into arms and legs. The proliferation of the cells triggers genes in the limb bud, which make proteins that sculpt the limb. CPS49, Dr. Vargesson argued, starves the limb, causing many cells to die. The surviving cells do not get the proper signals and fail to develop.

This model could account for how thalidomide could have such a drastic effect on limbs without causing much damage elsewhere in the body. Limbs develop relatively late, beginning about 23 days after the start of pregnancy. An embryo exposed to thalidomide at that point would suffer damage to its limbs, Dr. Vargesson said, while the rest of it would suffer less damage because its blood vessels were already mature.

Even if Dr. Vargesson’s model turned out to be right, it was missing some key pieces. In order for thalidomide to do its damage, it must grab on to some particular kind of molecule in the embryo.

To find that target, Dr. Hiroshi Handa of the Tokyo Institute of Technology and his colleagues coated microscopic beads with thalidomide. They then immersed the beads in various proteins. As they report in the current issue of Science, a protein known as cereblon latched on tightly to the thalidomide.

“We were very surprised,” Dr. Handa said. While scientists have identified scores of genes involved in the development of arms and legs, no one had ever suspected cereblon of playing a role. In fact, no one was sure what cereblon did.

To investigate cereblon further, Dr. Handa and his colleagues ran experiments on zebrafish embryos. The network of genes that builds zebrafish fins is almost identical to the one that builds human limbs. And, just as humans lose limbs, zebrafish lose fins when they are exposed to thalidomide.

The scientists speculated that thalidomide caused the defects by disabling cereblon proteins. They prevented zebrafish embryos from making cereblon, and, just as they predicted, the zebrafish could not grow fins.

If thalidomide could not bind to cereblon, Dr. Handa reasoned, it might lose its power. He and his colleagues tinkered with the gene for cereblon and discovered that if they altered it in two spots, it made a protein that thalidomide could no longer grab. They injected the altered cereblon into the wings of chick embryos along with thalidomide. The chicks grew relatively normal wings despite the thalidomide.

“This is a very important paper,” said Rolf Zeller of the University of Basel in Switzerland. “These findings were completely unexpected.”

He said that scientists now needed to see if thalidomide was also binding to proteins other than cereblon. “This study identifies a key piece of the 50-year-old puzzle behind the thalidomide tragedy, but it is premature to say ‘case closed,’ " Dr. Zeller said.
Now scientists have to figure out if thalidomide binding to cereblon is, in fact, the process that shuts down blood vessels. Dr. Handa, meanwhile, is investigating how cereblon controls the development of limbs.

Dr. Vargesson said the new results may point the way to new forms of thalidomide that can fight cancer or other diseases without attacking cereblon, and send phocomelia back to medical obscurity. “That,” said Dr. Vargesson, “would be the golden goal.”