The heroes of immune globulin production are many. They include physicians, scientists, and nurses, but most importantly, the patients who continue to seek new treatments and ask for alternative options.

Since the first practical use of serum immune globulin therapy for primary immune deficiency by Dr. Ogden Bruton in 1951, the use of immune globulins has evolved in the method of manufacture, the formulation and expanded applications for new diseases. Have newer products created these new uses or have new needs driven the creation of new products?

As the United States entered into WWII, the country recognized an untold number of American lives would be lost due to trauma, unless injured soldiers could be stabilized on the battlefield: The leading cause of death in combat was bleeding, which sent soldiers into shock before ever reaching the first medical aid station. However, the battlefield was no place to store fragile, refrigerated blood or whole plasma.

Because necessity is the mother of invention, Dr. Edwin J. Cohn, biochemist and protein scientist, saw the need to individually separate the many proteins in human plasma. Albumin, the chief protein constituent of plasma and one that Dr. Cohn had separated from plasma, could help solve this problem if it could be administered quickly. Albumin allows blood to remain in the blood vessels and is responsible for attracting water, thereby increasing blood volume. In addition to being a lifesaving protein, albumin could be freeze-dried and stored as a powder in the harshest of environments.

Once reconstituted, albumin could keep soldiers alive until they arrived behind the lines to mobile hospitals.

In 1941 the Department of the Navy commissioned Dr. Cohn to develop a large-scale process to separate albumin from human plasma, a process known as fractionation. Cohn’s invention led to the manufacture of more than 2 million units of albumin by approximately five U.S. manufacturers, and saved countless lives during the war. Plasma fractionation was a major factor in this improvement.

The invention of fractionation led to other new opportunities. Due to Cohn’s process, the use of purified immune globulin as a medical treatment became possible. The first human immune globulin preparations were administered as intramuscular (IM) injections, and could only be given in small doses. IM immune globulin (IMIG) injections were extremely painful, limiting the quantity of protein that could be administered. Nevertheless, such injections were a life-altering innovation for people suffering from antibody deficiencies, and there was a need for IMIG for these and other disease states.

Overcoming the obstacles to save and improve human life was the challenge of Dr. Ogden Bruton, an Army lieutenant colonel and a practicing pediatrician at Walter Reed Army Medical Center. Recognized as the “Father of Primary Immune Disease,” he successfully used IM formulations of immune globulins on Joseph S. Holtoner, an 8-year-old boy who presented with congenital agammaglobulinemia. Bruton administered the immune globulin just under the skin, subcutaneous administration. Dr. Charles A. Janeway Jr., a leading immunologist from Harvard School of Medicine, picked up on Bruton’s work and established IM dosages of immune globulins as a standard of care for primary immune deficiency diseases (PIDD) in the United States.

Although the quantities of immune globulins that were given at that time were low by today’s standards, fewer infections were seen in PIDD patients, and survival was enhanced. Between 1950 and 1960, with immune globulin injections as the standard therapy, the quality of life improved for PIDD patients.

With this advancement, new applications for immune globulins were explored using higher doses. However, purification of immune globulin from plasma was still in its early stages and higher doses resulted in a corresponding increase in the rates of adverse events. What was needed was the ability to deliver large quantities of purified protein in an acceptable dosage formulation.

Once again, manufacturing adapted to meet patient and healthcare providers’ needs. It wasn’t easy, though. The technology and equipment for large-scale operations was not available, and product formulations had to be improved.
not only to eliminate harmful side effects, but also to improve the stability of the product. These challenges were overcome in the late 1970s when the first generation of intravenous immune globulins (IVIG) was born. These “first gen” IVIGs gave patients the ability to receive large amounts of immune globulin. As expected, PIDD patients experienced fewer infections. Serendipitously, the ability to give these greater doses also led to the observation that giving IVIG to patients with leukemia and antibody deficiency also increased their platelet counts. This was followed by the observation that high doses of IVIG, given concurrently with aspirin therapy, had lifesaving effects in Kawasaki syndrome, an inflammation of the blood vessels that caused heart attacks and was often fatal in childhood. Thus, the beneficial effects of IVIG on the quality of life were extended to new, previously untreated diseases.

While the first gen IVIGs were a great improvement for patients over the IM formulation, there were still problems. For instance, manufacturers used pepsin, a naturally occurring enzyme, to break apart the protein aggregates. This enzyme decreased the immune globulin activity. To overcome the hurdles of decreased activity caused by the chemical modifications associated with enzymes such as pepsin, second generation IVIG products were introduced in the mid-1980s. These products did not use pepsin but instead added sugars or amino acids to make the products more easily tolerated in large dosages. In addition, one manufacturer lowered the pH of the product to increase the immune globulins’ natural stability. As a result, patients could receive large quantities of IVIG with fewer side effects.

High-dose applications of IVIG introduced in the 1980s marked a new age for patient care. Unfortunately, two new healthcare catastrophes came right on the heels of this latest improvement: the AIDS and hepatitis C epidemics. Since IVIG is a plasma-derived product, the possibility of virus transmission became a major concern because it was uncertain how the viruses were transmitted and how to test for their presence in IVIG. The introduction of a new generation of products was needed to address a higher standard of safety, thus the third generation of IVIG products was born.

The third gen IVIGs included steps such as solvent-detergent and pasteurization to increase safety by specifically removing or destroying unwanted organisms such as potentially harmful viruses, without compromising the quality of the life-giving protein needed for patient therapy. In the 1990s, the third generation products became the new standard in the United States, and improved patient care has resulted.

Now, in the 21st century, the fourth generation of IVIG products has been born, yielding greater convenience, higher tolerability and improved patient safety.

Leading immunologist, Melvin Berger, MD, PhD, co-author of this article, recently remarked, “We are fortunate that improved treatments for patients with [PIDD] continue to evolve. We have seen each generation of immunoglobulin preparations becoming safer and better tolerated by the patient. Newer products have decreased adverse effects, and allow increased flexibility in dosing, which together improve the quality of life for those whose survival depends on this essential therapy.”

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Melvin Berger, MD, PhD, is Professor of Pediatrics and Pathology, Case Western Reserve University, Ohio. Alberto Martinez, MD, is President and CEO of Talecris Biotherapeutics.

A Brief History of Immune Globulin

By Nicole Criona

As early as the 1890s, physicians were experimenting with blood product transfusions on animals, but they were generally unsuccessful because they weren’t yet aware of such things as blood type compatibility.

In 1901, Austrian researcher Karl Landsteiner discovered that blood drawn from certain people, when combined, tended to clump, while others did not. His work led to the discovery of blood types (A, B and O) and blood type compatibility.

It wasn’t until the 1940s that Dr. Edwin Cohn and his associates invented a large-scale method to separate the components of human plasma, called fractionation. This early method used a combination of alcohol, low temperatures and centrifuges to fractionate the plasma into its components, including immunoglobulins.

At first, immune globulin was administered intramuscularly. “It was painful to get,” said Dr. Richard Schiff, MD, PhD, global medical director for immune therapy and critical care at Baxter, an IVIG manufacturer. “However the incidence of severe infections plummeted.”

These early preparations of immunoglobulin needed to be administered into the skin or muscle due to clumps of antibodies resulting from the fractionation process. These clumps, also called aggregates, resulted in serious reactions if administered directly into a vein. This unfortunate experience was recorded by Dr. Janeway in 1946 during the testing of an initial immunoglobulin preparation on himself. After administering the immunoglobulin into his vein, he had to be treated for a serious reaction.

Fortunately, by the 1960s, the Swiss Red Cross began experimenting with preventing clumping of the IgG molecules with a gentle enzyme treatment. As a result, one of the first viable intravenous products was developed.

In 1973, researchers and physicians began the first U.S. clinical trials, testing the efficacy of IVIG. Eventually, the U.S. firm Cutter Biologics developed an IVIG product in which clumping was prevented by chemical treatment of the IgG molecule. This led to the first U.S. product in 1981, and then companies all over the world were trying to manufacture IVIG.

 Concurrently, safety became a grave concern with the recognition of blood-borne viruses. However, the alcohols used in the original immunoglobulin purification process destroy many viruses and patients receiving immunoglobulin during the early years of the HIV epidemic were spared product-related transmission. Other viruses, however, could survive the process and “the 1990s saw an increase in improved protection against viruses,” Dr. Schiff said. “The New York blood bank perfected a process which used a solvent detergent to break open certain viruses and became effective against what are called ‘envelope viruses’ such as West Nile Virus, SARS and HIV.”

The virus-fighting processes have since become a standard part of the process, and today IVIG is considered quite safe.