Percy Lavon Julian PhD — The Man Who Wouldn't Give Up

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In the Volume 2, Issue 1 of this journal, I told the story of Vivien Thomas, an incredibly bright and technically adept laboratory technician who had to take a role behind the physician Alfred Blalock, literally in the operating room where he would tell Dr. Blalock how to proceed in the new open heart surgeries Vivien developed, and throughout his whole life as he struggled as a black man in the scientific world. He is indeed a scientific hero worthy of honor for Black History Month.

Let me tell you the story of another black pioneer in health care science that has touched millions of lives but who you may never have heard of, and while February was officially Black History month, we should consider any month or day a good time to honor great scientists of all backgrounds. The scientists I will tell you about now will be of particular interest to neuromuscular health care researchers and providers.

Percy Lavon Julian, PhD was born in Montgomery, Alabama in 1899, the son of a railway mail clerk and the grandson of slaves. He was one of six children. His father and mother also worked as schoolteachers and filled their house with books for their children. His grandfather had lost two fingers as punishment for daring to read and write. His grandmother was known to pick more than 350 pounds of cotton a day. Julian attended the State Normal School for Negroes where he excelled, graduating at the top of his class. This was a school with the goal of training teachers and provided the equivalent of a tenth grade education. He told a story that a white policeman chased Percy from a fence as he watched young white boys conducting chemistry experiments in a school he could not attend because he was black. He also experienced coming across a black man in the woods near his house that had been lynched a few hours before. He then was admitted to DePauw University in Greencastle, Indiana as a sub freshman. DePauw admitted a handful of black students but required they simultaneously take additional high school classes to catch up with the white students. He had to take additional high school courses the first two years to fill in the gaps of his Alabama education, along with the full load of freshman classes. He also worked as a waiter in a white fraternity house and lived in the attic.

The Dean tried to discourage him from going into science, but he persisted, and he graduated first in his class,

Figure 1. Percy Julian is seen here in this 1920 photo at DePauw University.

and was that year's valedictorian, majoring in chemistry.

He applied to graduate school at DePauw and at many other institutions around the country, but he was denied admission. In 1960 he told this story as follows:

> I shall never forget the week of anxious waiting in 1920 to see if I could get to graduate school. I had worked hard for four years. I stood by as day by day my fellow students in Chemistry came by saying, "I am going to Illinois"; "I am going to Ohio State"; "I am going to Michigan"; "I am going to Yale.". "Where are you going?" they asked, and they answered for me, "You must be getting the Harvard plum." I could stand the suspense no longer. I went to Professor Blanchard, as staunch a friend as he knew how to be, and certainly later my most unforgettable friend, and asked timidly, "Professor, did you get me a fellowship?" And then this dear fellow with resignation told me "Now, now, Julian I knew you would be asking me that. Come into my office." There he showed me numerous letters from men who had really meant God to me- great American chemists of their day. And they had written to him, "I'll take your Mr..., but I'd advise you to discourage your bright colored lad. We couldn't get him a job when he's done, and it'll only mean frustration. In industry, research demands co-work, and white boys would so sabotage his work that an industrial research leader would go crazy! And of course, we couldn't find him a job as a teacher in a white university. Why don't you find him a teaching job in a Negro college in the South?

He doesn't need a P.D for that!" There went my dreams and hopes for four years, and as I pressed my lips to hold back the tears. I remembered my breeding, braced myself and thanked him for thinking of me.

So he took a position teaching chemistry for two years at Fisk University, a historic black university. He won an Austin Fellowship to attend Harvard where he obtained a master's degree in organic chemistry, again graduating at the top of his class. But while others were offered jobs as teaching assistants, Julian was not and he was told by Harvard officials that southern white students would be offended by being taught by an African American. By not being able to be a teaching assistant he could not go onto obtaining his PhD as he had no way to financially support himself. So Julian went to the West Virginia College for Negroes to teach chemistry. After only a year he moved to yet another historic black institution, Howard University as an associate professor of chemistry. His research involved the potential of using the ingredients of soybeans as a potential medical compound. In 1929 he was awarded a Rockefeller Foundation fellowship grant to study in Vienna, Austria, and there he completed his PhD in organic chemistry. He studied natural products chemistry. In 1931 he returned to Howard University as the head of the chemistry department. Dr. Josef Pikl, a Viennese colleague who he began working with as a doctoral student, also moved to Howard so they could continue working together.

Then DePauw University, which had previously rejected his graduate school application, asked him to return as a research fellow along with Dr. Pikl. From 1932 to 1935, they focused on coming up with a way to synthesize the compound physostigmine. This compound was first isolated from the Calabar bean in the 1800s. Extracts from the Calabar bean were shown to reduce intraocular pressure in the eye caused by glaucoma by causing the pupil to constrict and by doing so improves drainage of intraocular fluid. As early as 1864 the active ingredient was shown to be physostigmine. But no one had figured out how to synthetically make the compound and this was necessary to be able to provide a less expensive and larger supply of the drug. Julian and Pikl published a series of amazing papers in scientific journals culminating in the pivotal 1935 publication: "Studies in the Indole Series V. The complete Synthesis of Physostigmine (Eserine)". They utilized a team science approach that incorporated several undergraduate DePauw students. They were also in a race with a chemistry team of superstars in Oxford, England. The prestigious Oxford group published a paper around the same time saying they had manufactured the compound. But Percy believed the Oxford method was faulty and he challenged their process, and his teams results prevailed. This was the first complete synthesis of what is known in chemistry as an indole alkaloid. Since then, physostigmine and its many derivative compounds have been used to treat glaucoma and help literally millions of patients with this disorder, which can cause loss of vision.

It turns out physostigmine is very helpful for another much rarer condition called myasthenia gravis. This is a rare disorder of skeletal muscle and it is one of the diseases that I specialize in. With myasthenia, patients become weak because they make autoantibodies that block the acetylcholine receptor in muscle so the signal from the nerve carried by the compound acetylcholine to activate the muscle is blocked. One way to overcome the block is to prevent the acetylcholine from being degraded. It turns out physostigmine does exactly that and if you give a myasthenia gravis patient physostigmine their muscles become stronger. This was first discovered in 1934 using naturally occurring physostigmine by a young British physician named Mary Walker and it was a major breakthrough in the treatment of myasthenia gravis. But obtaining naturally occurring physostigmine was just as difficult to obtain for myasthenia gravis patients as it was for glaucoma patients. Once this compound could be made synthetically using the discovery of Julian and colleagues, physostigmine and its derivatives became the standard treat for myasthenia gravis. I still use a related drug called pyridostigmine in almost all of my myasthenia gravis patients. This all is due to Dr. Julian and his team. Other drugs that are derivatives of physostigmine are used for many other conditions. The class of drugs currently used to treat Alzheimer's disease (Aracept, Exelon and Razadyne) are derivatives of physostigmine.

The discovery of how to manufacture physostigmine is definitely the most important scientific discovery to ever come from the DePauw University laboratories. The research fellowship funding had come to an end in 1935 and Dr. Julian was proposed to be the chair of the chemistry department. But he was not offered the position as some of DePauw's staff objected to working for an African American.

He was offered a position as a researcher at the Institute of Paper Chemistry in Appleton, Wisconsin. The head of the institute visited Dr. Julian at DePauw and they made plans for the research projects he would work on. But just before

he was to move it was discovered that an old city statue of Appleton prohibited the "housing of a Negro overnight". He could not live in Appleton!

So he left for the world of industry and he took a position with the Glidden Company, becoming their chief chemist and Director of Research. He moved to Chicago. There, he became an expert in soybean products and developed pathways to synthesize numerous substances starting from soy-based ingredients. His laboratory was the first to extract the proteins from soybeans which he called the "Alpha" Proteins, and this became the basis for dozens of home and food products. But he and his family continued to be confronted by racism in the north. One Thanksgiving Day arsonists tried to burn down Dr. Julian's new home in Oak Park, an exclusive white suburb (the hometown of Ernest Hemingway). On another occasion someone hurled a dynamite bomb into the house, but no one was injured. He and his son often felt it necessary to stand sentry duty around their home with shotguns.

His career in the Glidden company was spectacular. He discovered a protein in soybeans that could be used to coat paper and make it less flammable. This was then made into a fire-retardant foam that could be packaged in canisters and sprayed on fires. It was used extensively on ships in World War II and it is estimated that it saved the lives of thousands of sailors. It was called Julian's "Bean Soup".

While still at DePauw, Dr. Julian had discovered the steroid stigmasterol was created as a byproduct of physostigmine isolation from the Calabar bean. This was a serendipitous discovery, a byproduct of his search for a way to synthesize physostigmine. Stigmasterol is a steroid and has a similar structure of many biologically significant compounds such as cholesterol and the sex hormones progesterone, estradiol, and testosterone. The science of steroids such as progesterone and other sex hormones was being developed in a number of laboratories and clinics around the world in the 1930s and subsequent decades. Progesterone was found to be useful in helping pregnant women avoid miscarriages. While at DePauw he had actually written the Glidden company to ask for extracts of their soybean oil so he could pursue work on trying to isolate these compounds from soybean. Instead Glidden hired him!

At Glidden, as the director of research in the Soya Products Division, one day he was asked to go to the large soybean oil storage tanks because water had seeped into the oil and resulted in the formation of a white solid material at the bottom of the tank. Dr. Julian figured out that this material was stigmasteroid and he realized he had stumbled on a method for producing large amounts of the steroid from soybeans. He then figured out how to synthesize progesterone from stigmasterol on a massive scale. Soon Glidden was producing 5 to 6 pounds of progesterone a day and soon after other sex hormones were in production. The Readers Digest Magazine did an article about Dr. Julian in 1946 titled "The Man who Wouldn't Give Up."

But Julian was not done finding amazing new uses for soybeans. In 1949 at the Mayo Clinic, cortisone was first used to treat patients with rheumatoid arthritis. It worked like a miracle. Bedridden patients could walk again. The Mayo doctors, Hench and Kendall, received the Nobel prize for their discovery in 1950. They extracted cortisone from the adrenal glands. The chemical extraction was laborious and expensive. An ounce of cortisone cost $4,000 in 1949 dollars. As the word spread around the world of this discovery, Dr. Julian had a flash

of inspiration: to synthesize a substance very close to cortisone, called cortexolone, from soybean derivatives. This was called "substance S" and it could be easily converted to cortisol, also known as hydrocortisone and then to cortisone. This was a huge breakthrough. This led the way to a low-cost production of these compounds. Dr. Julian was honored as Chicagoan of the Year in 1950 for this discovery.

I use prednisone as a mainstay for treating autoimmune neuromuscular disorders such as myasthenia gravis, polymyositis, and inflammatory neuropathy. While we all know of the side effects that can come from cortisone derived drugs, they are life saving for millions of patients.

Intravenous solumedrol is used in caring for COVID-19 patients in the intensive care unit. Asthma patients depend on steroid inhalation therapies as well as oral steroids. If you buy over- the-counter 1% hydrocortisone cream at your local drug store or grocery for a rash, you are benefiting from Dr. Julian's discoveries.

Others then discovered that Mexican yams (yes, the potato!) were a plentiful source of steroid precursors that could lead to progesterone and other steroids. Julian tried to convince the leaders at Glidden to stop manufacturing steroids from soybeans and switch to Mexican yams. This was a step too much for the paint company! So Julian left Glidden in 1954 and set up Julian Laboratories, initially located in Chicago and then he opened Laboratoires de Julian de Mexico near Mexico City. He was ready to enter the field of competitive steroid production in a big way.

But... there was politics to deal with and the Mexican government would not allow Julian to harvest the yams he

needed. Julian did not give up and a man named Abraham Zlotnik came to his aid. Julian met Mr. Zlotnik in Austria and helped him escape from Nazi Germany. Now Zlotnik wanted to return the favor. He told Julian the same yams were readily available in Guatemala and he arranged for a steady supply of tubers to be send from Guatemala to Mexico. In subsequent years Julian's further breakthroughs were made so that they could quadruple the production of steroids from yams. Rather than increasing their profit margin, Julian insisted the company reduce the price of synthesized drugs like progesterone from $4,400 a kilo to $400 a kilo and the drugs became even more available.

In 1961 Julian sold his laboratory to Smith, Klein and French for $2.5 million dollars and he was one of the richest black men in America. He retired from business, spending time as a public speaker and he remained socially active seeking to advance the conditions for blacks, helping to fund the Legal Defense and Educational Fund of Chicago. He raised money for the NAACP Legal Defense and Educational Fund throughout the country. He financially supported Dr. Martin Luther King Jr. and the Southern Christian Leadership Conference. He said, "All Negros identify with the civil rights movement because none, no matter what his income level, can escape racial discrimination." He served on the board for Howard University, Fisk University, Roosevelt University and Southern Union College, the Chicago Theological Seminary, the State of Illinois Colleges and Universities, the NAACP Legal Defense and Educational Fund and the Center for the Studies of Democratic Institutions. In 1967 Dr. Julian was appointed to the DePauw University Board of Trustees! He was a Fellow of the American Institute of Christ, of the Chemical Society of London and of the New York Academy of Science. He was voted into the National Academy of Sciences in 1973.

Figure 2. In 1993 the US Postal Service issued a stamp honoring Percy Julian for Black Heritage USA.

In 1972 a new Science and Mathematics center was opened at DePauw and Percy Julian gave the dedication address "Science and the Good Life of Man." Dr. Percy Lavon Julian, the man who would not give up, died in 1975 of liver cancer, possibly caused by the many dangerous solvents and chemicals to which he had been exposed. Following his death, DePauw University named the Percy L. Julian Science and Mathematics Center in his honor.

I would like to quote remarks by Dr. Julian regarding racial issues facing black scientists:

"The ghetto gloom of apartheid is slowly but surely fading on the horizon. And a completely new day is dawning for the hitherto schizophrenic Negro scientist. As he is finding his way into university faculties, where his creative talents may find uninhibited outlet, his total intellectual integrity is taking mastery over the frustrating necessity to bolster his own waning spirits. He is slowing arriving; he has faith in himself; and he is becoming a calm, determined scholar – eager, anxious, and definitely destined to write new chapters in the history of discipline. Indeed he is doing so already!...The Negro scientist now need neither starve nor be condemned to a frustrating intellectual ghetto if he chooses pure science as a career." "It will be exciting to see the success of this new Negro intellectual in passing his experience and rebirth on to the less fortunate among his fellow men."

He was such a remarkable man, but I did not know about Dr. Julian until very recently. I wrote an article that included a history of the use of physostigmine and similar drugs for myasthenia gravis and my research did not turn up his name. But then I began researching the early use of steroid drugs for myasthenia gravis and I began reading on the discovery of cortisone and the first miraculous treatment of rheumatoid arthritis patients at the Mayo Clinic. In the book *The Quest for Cortisone* I learned the role of Dr. Julian and it also told of his earlier role in the synthesis of physostigmine. Who knew? Not me. But it turns out PBS knew! After I wrote this EVC message, my Sr. Executive Assistant, Amanda Sebok, discovered that a bio-documentary about Dr. Julian was made by PBS in 2007! I just watched it this week and learned much about Percy Lavon Julian. Check out this amazing video and learn about the dozens of other soy products his Glidden team invented. From soy-based paint, cosmetics, salad oils, margarine, plastics, linoleum, dog food, and soy cheese.

Dr. Julian is an inspirational and accomplished scientist worthy of even more renown. Here is to Percy Lavon Julian, PhD in Black History Month and beyond... son of the south and benefactor to the world through his many discoveries. And, like me until very recently, I bet many of you did not

know this story so I am so glad to be able to tell you about Dr. Julian.

Rick

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