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In Memoriam

Paul H. Patterson (October 22, 1943 — June 25, 2014)

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This year we lost a leader in the field of Huntington's disease research, Dr. Paul H. Patterson, a visionary scientist who made an impact on everyone he met with his wit, charm, creativity and novel insights. Here are some personal recollections and thoughts about Paul from two of us who knew him very well.

In Memory of Paul H. Patterson

By Amber L. Southwell

Eminent Caltech neuroscientist, Paul H. Patterson, died on June 25, 2014 as a result of glioblastoma multiforme. He is survived by wife, Carolyn, and son, Paul Claire, both great sources of joy for him. Paul's numerous personal and scientific contributions will long outlast his tenure in life. Being both an amazing scientist and human being, Paul influenced and inspired countless friends, collaborators, and trainees, among whose number I am proud to count myself.

To talk about Paul as a scientist, I need to go back to 1977. 1977 was a great year. The Sex Pistols were rockin' the world, Apple computers was incorporating, and Paul was at Harvard where he discovered that mature neurons could change their neurotransmitter identify in response to external factors [1, 2]. This finding challenged the "one neuron, one transmitter" dogma of the day and initiated divergent branches of neuroscience. Paul went on to discover that the cytokine, leukemia inhibitory factor, or LIF, could induce production of acetylcholine in cultured rat sympathetic neurons [3]. This finding, that immune system molecules could influence the development and behavior of neurons, formed the basis for the field of neuroimmunology, in which Paul continued to work. Over the years, Paul and his team studied the effects of LIF on CNS cells and demonstrated that it could promote neural stem cell self- renewal in the adult brain [4], oligodendrocyte survival after spinal cord injury [5], and remyelination in an acute model of multiple sclerosis [6], identifying LIF as a powerful potential therapeutic with protective and restorative capabilities.

In parallel, Paul investigated immune involvement in neurodevelopmental disorders, such as schizophrenia and autism. Epidemiological data following viral outbreaks had shown that multiple types of infection

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during the second trimester of pregnancy can lead to increased risk of neurodevelopmental disorders in the offspring. Paul reasoned that the common factor in these various infections was not the pathogen, but the maternal immune response [7], so he began to study maternal immune activation in mice. This may seem an obvious choice today, because the study of neuropsychiatric disorders in mice is commonplace now. However, at the time, this was relatively rare. Even when I came to Caltech in 2001 there were some who snickered on the way out of the seminar room at the idea of modeling complex psychiatric behaviors in mice, but Paul was not the kind of man to be influenced by things like that. He and his team were among the pioneers of psychiatric testing in mice and their perseverance made the work that I, and many others, do today possible. Through their investigations, Paul and his team demonstrated that influenza infection in pregnant dams can induce abnormal behavior in the offspring [8], though no virus is detected in fetal tissues [9], indicating that Paul's hunch was likely correct. They went on to show that the synthetic dsRNA poly(I:C), which mimics viral infection and activates the host immune system, could induce the core symptoms of autism and relevant structural changes in the brains of the offspring of dams treated during pregnancy [10, 11]. Having confirmed that the maternal immune response was indeed the culprit, the next challenge was to find the mechanism. Paul and his team determined that maternal IL-6, a pro- inflammatory cytokine, was both necessary and sufficient to alter fetal brain development, and induce schizophrenia and autism like neuropathology and behaviors in the offspring of immune activated mothers [12]. Paul then used this maternal infection model to evaluate many aspects of neurodevelopmental disorders in the search for effective therapy. He and his team showed that the offspring of immune activated dams have permanent immune dysregulation including elevated IL-6 [13] and that, like children with autism spectrum disorders, they have a leaky gut and altered gut biota. In a recent landmark study, they showed that treating the post-development offspring of immune activated mothers with probiotics could normalize the gut epithelia and microbiome and, incredibly, restore normal behavior in mice [14]. Right up until his death, Paul worked tirelessly to translate these findings into a clinical trial of probiotics for children with autism spectrum disorders. While he did not survive to see this become a reality, this work will be a vital part of Paul's legacy.

This is only one example of Paul's deep commitment to the study of human disease. During the time that I was in his lab, Paul worked toward understanding and therapy development for Alzheimer disease, autism, schizophrenia, multiple sclerosis, spinal cord injury, cancer, and Huntington disease. Paul's focus on the study of disease made him a bit unconventional at Caltech, which is an incredible and unique place but which is also very basic science oriented. Paul pioneered the MD/PhD program at Caltech in partnerships with UCLA and USC. As a result, pretty much every student interested in medicine came through our lab at some point. We had so many undergraduates in the summer that we called it Camp Patterson.

Paul was fiercely dedicated to solving Huntington disease. He was a member of the Hereditary Disease Foundation (HDF) scientific advisory board from 1991 until his death. The MW series of monoclonal anti-huntingtin antibodies that Paul's lab developed and named for HDF founder Milton Wexler [15], were critical to the study of the structure and function of the huntingtin protein [16–18]. At my first HDF meeting in 2004, Paul gave a talk and then sat on a panel where some of the recently identified functions of the huntingtin protein were being discussed. At one point Paul said "I think it's time we all take that sentence out of our introductions that says huntingtin is a large protein of unknown function". The audience erupted in applause and someone stood up and yelled "I vote for Paul". That was the moment I knew that Paul was a rock star! Paul and his team also found that the transcription factor, NFκB, was overactive in HD [19], identifying a, at the time, novel pathogenic pathway comprising a host of potential therapeutic targets. Additionally, Paul and I worked together to develop an intrabody gene therapy for HD from conception, screening and characterizing, through pre-clinical testing [20–22]. Paul was an amazing mentor who guided me expertly through every stage of this ambitious thesis project. His mentoring style was hands off but available. He pretty much let me do my own thing unless I came to him, but his door was always open, he never failed to remove a roadblock that I laid at his feet, and he was always interested to hear what I had to say. In addition to helping me reach my experimental goals, he also taught me to think for myself, to question what I read, to look at the big picture, to write concisely but with eloquence, to present clearly but comprehensively, and to acknowledge graciously. Paul also had a great sense of humor, which is a wonderful thing in a mentor. He was fun, and he wasn't afraid to be silly. We laughed a lot.

The last time I saw Paul was at the 2013 Patterson lab reunion dinner at the Society for Neuroscience meeting. We could all tell that something was wrong with

Paul, but like most Patterson lab events, that evening was centered around excellent food, good friends, and laughter. About a month later when I emailed Paul for advice about his holiday eggnog recipe "are you sure there's really supposed to be that much liquor in it?" I got a reply from his wife, Carolyn, telling me that he had brain cancer. Maybe it was worse because I opened the email expecting eggnog advice, but I felt like I'd been punched in the gut. In true Paul style, he faced this final challenge as a scientist. He presented a lab meeting about his disease showing MRIs of his tumor, and he dedicated the rest of his life and his body to a dendritic cell vaccination trial at UCLA to try to help others with this intractable and insidious disease.

Caltech recently held a symposium in honor of Paul's life and career. Sadly he died just 4 days before the event, so it was in a way his memorial. Each of the speakers, who had mostly been Paul's trainees, began with photos and personal anecdotes about Paul with topics ranging from feminism to food and conspiracy theories, they then proceeded to talk about their own scientific work. Paul would have loved the combination of laughter and great science.

I'm greatly saddened not to have Paul's guidance moving forward, but I am truly grateful to have had him in my life. He shaped my career and my life by continually demonstrating unyielding scientific integrity with generous side helpings of both irreverence and diplomacy. I will always remember the many lessons that he taught me and strive to be the kind of scientist and the kind of person that he would be proud of.

A Tribute To Paul H. Patterson

By Nancy S. Wexler

I met Paul H. Patterson more than 30 years ago. He was tall, had long blonde hair tied into a ponytail and piercing, large blue eyes. Paul had a wonderful sense of humor. His eyes and mouth were always laughing with outright merriment or with a hint of amusement. Paul studied as a postdoctoral student at Harvard Medical School and joined Harvard's faculty. In 1983, Caltech wooed him away to California, where he remained until his death. We invited him to join the Science Advisory Board of the Hereditary Disease Foundation. Paul served as an innovative and catalytic Board member until the day of his death.

Mercurial and brilliant, Paul pushed the edges of science, even during his postdoctoral research and ever since. Paul challenged the conventional wisdom that cells could only grow in particular media in response to special cues. Paul proved that cells are plastic if you give them the right recipes for growth.

Paul admired my Dad, Milton Wexler, who founded the Hereditary Disease Foundation in 1968. He was Chairman of the Board until he died in 2007. Paul and my Dad stood eye-to-eye, both with piercing blue eyes. When Paul had a spectacular breakthrough in science, he named them after my Dad. Paul created the Milton Wexler Monoclonal Antibodies! As the extraordinary dancer he was, Paul did a slow tango around the mutant huntingtin protein, looking for ways to envelope it. Each antibody he developed against mutant huntingtin deftly swooped over one part of the protein and identified it. Paul had the brilliant insight to use these antibodies themselves to attack the abnormal protein from inside the cell. He called them "intrabodies" because they work inside the cell. Paul was creating a special delivery system to get his intrabodies into cells. These "carrier pigeons" are made up of viruses, with the healing intrabody inserted to be delivered to wherever necessary. Testing these antibodies in mice has showed great promise.

Paul was a spectacular mentor, teacher and friend. He trained many talented, innovative students who have spread across the world to impact science. Paul combined rigor and creativity – always thinking out of the box. He found the evidence to support his theories, even when they went against the popular grain. He published his book: Infectious Behavior: Brain- Immune Connections in Autism, Schizophrenia and Depression. In it, he carefully explained his evidence and gave suggestions for treatments. Paul leapt into the future by collaborating on a potential new therapy for autism.

Paul H. Patterson was a renaissance scientist. His wife Carolyn, his son Paul Clair and all of us will miss his touch profoundly!

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