John Jacob Wasmuth (1946-1995)

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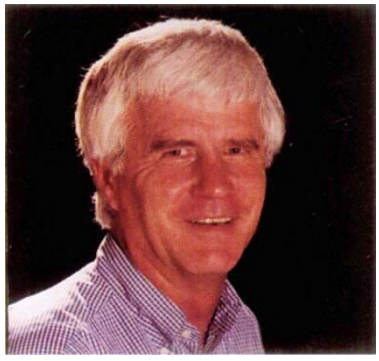
Two years ago, John Wasmuth fell in love with his new grandson, Connor Bones. John asked my sister Alice to inscribe her book (*A Memoir of Family, Risk, and Genetic Research*)'To Connor, whose grandfather was a gene hunter.' As Connor will discover, John was not only a gene hunter — and finder — but a gifted, imaginative, charismatic and humane man whose contributions to science and society have been extraordinary. Connor will be proud.

John Wasmuth died on December 29, 1995. A biochemist by training, John had been a pioneer among that very select group that began their genetic investigations when the terrain was untraversed and inhospitable. John helped develop positional cloning strategies that were used by his own group and others worldwide to identify genes. John became a wizard in somatic cell genetics. He had a particularly deft hand at creating human-rodent hybrids that enabled him to isolate a single human chromosome against a rodent background. His mountains were chromosomes 4 and 5 and he explored these two territories throughout his productive career, discovering many of the treasures these chromosomes have to offer.

John grew up in Greenville, Illinois. His father was a grocer, his mother a registered nurse. A Bachelor of Arts in biology in 1968 from Southern Illinois University made John the first in his family to earn a college degree. He went on to earn a Ph.D in 1973 in molecular biology at Purdue University under the direction of H.E. Umbarger, and spent the next three years as a postdoctoral fellow with Tom Caskey at Baylor College of Medicine. John was studying amino acid analogues to select for resistant cell lines as a way of approaching amino acid regulation in mammalian cells. He developed a system for selecting chromosome-specific panels that made him a leader when he later began searching for disease genes. John joined the Department of Biological Chemistry at the University of California, Irvine, in 1977, where he became Professor and Vice Chairman. The University has just awarded him a Distinguished Faculty Lectureship Award for Research, one among many distinctions including the Research Achievement Award, (UCI, 1988), Co-Recipient National Medical Research Award (National Health Council, 1993), Milton Wexler Research Award (Huntington's Disease Society of America, 1993).

Genes were never abstract entities for John, but the mechanisms for alleviating human suffering from genetic disease. In 1983, John isolated and



characterized a hybrid containing human chromosome 4 alone. Later that year, the Huntington's disease (HD) gene was localized to the short arm of that chromosome. John's expertise in somatic cell genetics and his creation of this precious resource made him a natural to become involved with the search for the HD gene.

John participated in the very first workshop following the localization of the HD gene convened by the Hereditary Disease Foundation in January, 1984, to launch the search for the gene itself. At the close of the workshop, John announced that he would share his chromosome-4 hybrid with the group. With the enormous amount of genetic material to be searched threatening to capsize the project before it had begun, John's gracious gesture was a vital first step to launching the effort. The group organized a formal collaboration called the Huntington's Disease Collaborative Research Group. John's fellow principal investigators were Francis Collins, James Gusella, Peter Harper, David Housman and Hans Lehrach, along with 52 international scientists.

Then a fateful piece of information came John's way. Because of his interest in cri du chat syndrome — a severe developmental defect in children caused by a deletion of part of the short arm of chromosome 5 — he learned of a chromosome that had the tip of chromosome 4 translocated onto the tip of chromosome 5. This unique sample could not be recollected and all depended on John's talent in making hybrids. He created what became the ultimate cell line for doing experiments, HHW693, containing just the piece of chromosome 4 that housed the HD gene.

Only after John was certain that his cell line was viable would he agree to accept grant money from the Hereditary Disease Foundation for the work. Then he created a recombinant DNA library from it and began isolating DNA clones. In order to pinpoint the location of the HD gene, John developed a somatic cell mapping panel consisting of cell lines of individuals with varying amounts of the tip of chromosome 4 deleted. By observing if *D4S10*, the only marker then linked to the HD gene, was retained or deleted, John could refine the obligate region containing the gene.

John was consistently a generous, supportive, creative and essential member of the Collaboration. One of my most vivid images is of Mike Altherr, a postdoctoral fellow working with John, coming to a workshop with his pockets stuffed with a crucial probe to hand out to the rest of the group. John did not know if he was handing out the gene; he just sat there smiling like a Cheshire cat. As it was, a particularly good marker of John's turned out to be extremely close to the gene and especially good for diagnostic testing, which gave added certainty in difficult situations.

Before the HD gene was found in 1993, my sister asked John how he would feel when the moment came. "Oh, I'll be ecstatic," he said. "It's just like reading a great mystery novel, you're up to the last chapter and it's been so involving and exciting you want it to continue, and yet you can't wait to find out who did it. At the same time, [when the gene is discovered,] I'll be a little bit sad because it's the end of the most exciting project that's ever gone on in my lab. Not the end — obviously there's so much more to do — but getting this far has been so

exciting and frustrating and taken so much effort that in a way it's going to be, not disappointment at having achieved it, but disappointment that that part of the effort is over. Almost like postpartum depression. Like Buzz Aldrin, the second guy to walk on the moon, says, 'Well, what the hell do I do now, I've walked on the moon, what's next?'" But when the HD Collaboration group finally discovered the gene in 1993 after a decade of arduaous searching, John said "Being part of the 'greatest gene hunt' in history means more to me than walking on the moon would have. I feel that I have had an experience that caused more emotional highs and lows than most people can even imagine — let alone feel first hand. I will never forget any part of it."

For the push through 4 million base pairs to find the HD gene, John had provided reagents, imagination, long hours, optimism and finally success was at hand. John met with scientists, physicians and families with HD to explain to them this extraordinary finding of an expanded repeat at the 5' end of a novel gene that coded for an immense protein called 'huntingtin'.

En route to finding the HD gene, John had isolated the gene for fibroblast growth factor receptor 3 (*FGFR3*). When the gene causing achondroplasia, the most common form of dwarfism, was localized close to the HD locus, John reasoned that the *FGFR3* gene would be a superb candidate for a problem with growth. Just five weeks later, he had proved his intuition: Mutations detected in *FGFR3* produced achondroplasia[2]. Some time later, his group found that additional mutations in the same gene cause a clinically related but lethal skeletal dysplasia called thanatophoric dysplasia[3].

A similar hunch led to the discovery of the gene causing hyperekplexia, or 'startle' disease, which causes an exaggerated response to being startled by sound or touch, even to the point of stiffening, falling over, or in newborns, death through apnea and aspiration. The gene for this autosomal dominant disorder was mapped to the long arm of chromosome 5. John, postdoctoral fellow Rita Shiang and their colleagues then mapped the glycine receptor gene into the same region. They immediately realized that glycine, as an inhibitory neurotransmitter allowing the muscle to relax following excitation, was a superb candidate gene. Their biochemical insight was again correct: mutations in the α_1 subunit of the glycine receptor were demonstrated to be the cause of the disease[4]. Unravelling the biology of this condition could lead to a better understanding of sudden infant death syndrome.

John's activities on chromosome 5 continued unabated, despite his conquests on its neighbouring chromosome. With Ray White in 1988, he localized a gene for familial adenomatous polyposis, a form of colon cancer. In 1994, he identified a portion of a gene for spinal muscular atrophy, a neuromuscular disorder that is the second most common lethal recessive disease among humans, and helped create a diagnostic test[5].

John's most recent gift to the world is the discovery of the gene causing Treacher Collins syndrome, described on page 130 of this issue[6]. Treacher Collins is an autosomal dominant disorder of craniofacial development. Once again, John and his colleagues have made history: no candidate gene guided their search, no chromosomal abnormality gave a clue and no obvious defect (such as an expanded trinucleotide repeat) told them they had arrived. Treacher Collins syndrome is the first autosomal dominant disorder captured through positional cloning alone, with each family's private mutation requiring independent analysis. Generous and cooperative at heart, John was willing to work again as part of a larger team, this time with Mike Dixon's group in Manchester, publishing as the Treacher Collins Collaborative Group. That the gene was named 'treacle' underscores John's wry humour and keen appreciation of the absurd!

John's biochemical insights have consistently led him to the discovery of new genes and these breakthroughs in turn allowed him to focus on the function and mechanisms of proteins found. John was immersed in the question of how these proteins cause their damage and how to prevent or treat the diseases that the genetic abnormalities he identified leave in their wake. However, John was not only preoccupied with finding and analysing individual disease genes, but with building the genomic infrastructure on which all gene discovery rests. Following extremely competitive review, in 1993 the National Center of Human Genome Research awarded John one of 16 Genome Science and Technology Centers nationwide. His centre focuses on building a physical map of chromosome 5.

John always understood the human context of his work. He was exquisitely sensitive to the urgency and despair of families with HD hosting them in his laboratory, serving on review boards, and giving people hope through witnessing his dedication. He understood the problematic nuances of presymptomatic and prenatal testing for HD and for dwarfism. When he discovered the gene for achondroplasia, his first concern was that the information would be misused to abort fetuses with a condition he viewed as part of the rich diversity of life. John interacted closely with the Little People of America to ensure that the test wold be used with least harm. John queried his role as a scientist, the responsibility of the discoverer for the use of the discovery.

He was an extraordinary mentor, of his own students and others, nurturing people while inspiring them to flourish independently. He encouraged them and was always proud of their successes. He was egalitarian and listened well, generous in giving credit, although loathe to receive it. John had a remarkable humility for one so accomplished. He talked almost diffidently about one impressive achievement after another. He could tease with a dry, acerbic wit but never hurtfully.

Prematurely silver haired, lithe, soft spoken, John had the infectious enthusiasms of a boy. He took his entire group to see 'Jurassic Park' when DNA went Hollywood, and had an autographed copy of Robin Cook's 'Mutation'. A tarpon caught at Islamorada, Florida, during one of the Collaborative HD Group meetings inspired many tall fish tales. He had a restive ebullience and you always knew when he was in the room.

John's acquaintance with sadness gave him empathy and compassion. His intelligence, warmth, ironic sense of humour and jubilance of spirit made him a magnet that drew us all near. He was extremely close to his family — his wife Judy, daughter Michele, son-in-law Matt and, of course, Connor. John's heart that stopped was big enough to encompass us all and more. We all miss him intensely. □

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2. Shiang, R. *et al. Cell* **78**, 335-342 (1994).
3. Tavormina, P.L. *et al. Nature Genet.* **9**, 321-328 (1995).
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6. The Treacher Collins Syndrome Collaborative Group *Nature Genet.* **12**, 130-136 (1996).