

OBITUARY

Victor Almon McKusick (1921–2008)

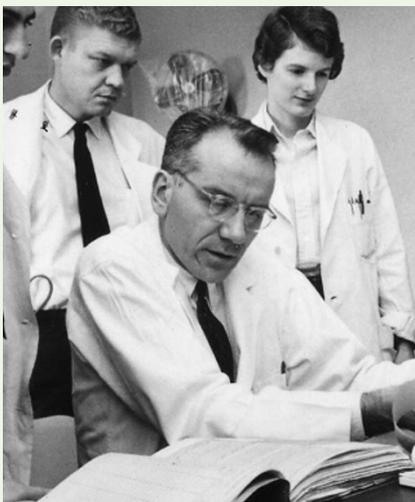
Quiet revolutionary in genetic medicine.

Following the complete sequencing of the human genome, we stand at the beginning of an era that promises medical treatments tailored to an individual's genetic make-up. No one is more responsible for this revolution than Victor McKusick, who died on 22 July. McKusick was the first to understand that systematically mapping human genes predisposing the bearer to disease, which many considered no better than stamp-collecting, was a route to a new medicine. In this and other ways he was instrumental in moulding the discipline that we now call genetic medicine, and in making genetics the basic science of medicine.

McKusick was born on a dairy farm in Maine in 1921. His early ambition was to enter the ministry. At the age of 15, however, a streptococcal infection of his arm that required a long hospital stay and treatment with one of the first antibiotics, made him rethink his future. His identical twin Vincent chose to study law. Victor, by contrast, after initial education at Tufts University, entered Johns Hopkins University in 1943 to pursue medical training, making a name for himself in cardiology.

Like medicine, genetics came to him by chance. His fascination with one teenage patient who suffered from intestinal polyps and melanin spots, and later with three members of a family who exhibited the same syndrome, provided him with first-hand experience of the basic principles of genetics. One was the need to recognize patterns of inheritance, in this case dominant as opposed to recessive, that suggested mutations at one genetic location. Another was the need to distinguish between mechanisms: in these patients, were two genes involved, one for polyps and one for spots, which were co-inherited (linkage), or were polyps and spots different manifestations of the same gene (pleiotropy)? McKusick was thus well armed when he subsequently came across patients with Marfan syndrome — with its dominant inheritance and remarkable pleiotropy affecting the aorta, eye and skeleton — which, he argued, arose from mutations in a single gene.

Similar patients and their families were to prove pivotal in his conversion to genetics, which was complete by 1957. Asked to direct a chronic-disease clinic by his boss, McKusick argued that “genetic disease is the ultimate chronic disease, since it's lifelong”, and seized the opportunity to reshape the Moore Clinic at Johns Hopkins to create the first unit devoted to medical genetics. He learnt his trade by doing: by using the rudimentary cytogenetic, biochemical and



population (quantitative) genetic methods then available. He soon became convinced of three guiding principles: the value of knowing a gene's location in the human genome; the value of accumulated genetic information; and the value of disseminating this new information widely and rapidly.

Given the individual rarity of most hereditary disorders, McKusick knew that he had to learn about the experiences of others and to share his own. He was a prolific organizer, of both ideas and facts, a trait most notably made manifest in 1966 in *Mendelian Inheritance in Man (MIM)*, the first edition of his catalogue of all known genes and genetic disorders. The final print edition appeared in 1998, but since 1987 it has also been available as full-text online, with a free database (www.ncbi.nlm.nih.gov/Omim). It now has some 19,000 entries, with more than 70% of the content having been produced by McKusick himself. This is his most lasting achievement — it is a deep resource and knowledge base, without which clinicians and any manner of biologist would be intellectually orphaned.

One of McKusick's preoccupations was with cataloguing the location of each human gene associated with a disease, and thus to create a disease map of the human genome. He did this not only through his own pioneering studies, but by beginning — chiefly with Frank Ruddle — a series of human gene-mapping workshops. Subsequently, he was an influential voice in organizing the international community around the Human Genome Organization (HUGO, fondly called Victor's HUGO). For him, the *raison d'être* of mapping, which he articulated in 1969, well before anyone understood or believed it, was that mapping all human genes was the best way to understand the basic malfunctions causing birth defects.

The existence of *MIM*, together with McKusick's mapping preoccupation, were the two most persuasive factors in favour of the public project to sequence the human genome. McKusick himself was on the US National Research Council committee that recommended the project, and was one of its prime cheer-leaders. He was among those who argued for a ‘map first, sequence later’ approach, and was a supporter of mapping and sequencing other species, and of tackling the whole genome rather than only the known functional genome.

As a pragmatist, however, McKusick was also attracted to Craig Venter's idea of sequencing expressed sequence tags (nucleic-acid snippets that encode only a portion of functional genes). He supported both the public sequencing project and Venter's private sequencing effort at Celera (he was a trustee of Venter's eponymous institute), because he believed that the genome could thus be completed sooner. The leaders of both the public and private sequencing ventures (Francis Collins and Venter, respectively) paid their respects at his funeral service.

McKusick made research on the human species, despite its poor genetic properties of few offspring and long generation times, a treasure trove for uncovering new genetic mechanisms. He also provided a glimpse of the future for genetic medicine in an interview given in 2001: “I think the medical geneticist will spend much more time overseeing gene screens, or genome screens, interpreting the results to individuals, and designing programs to make the most of the strong points of the genome and to avoid troubles from some of the weak points in the genome.” Spreading the word was a vital part of his legacy — as for example in the influential ‘Short Course’ in mammalian genetics, held annually at the Jackson Laboratory in Bar Harbor, Maine, which he founded in 1960 and co-directed.

In the long journey to his many accomplishments, Victor McKusick was accompanied by his rheumatologist wife Anne. Those accomplishments are all the more remarkable for having been achieved without his once raising his voice. But then a man who had genetics institutes named after him in Baltimore, Bologna and Beijing had no need to draw attention to himself.

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