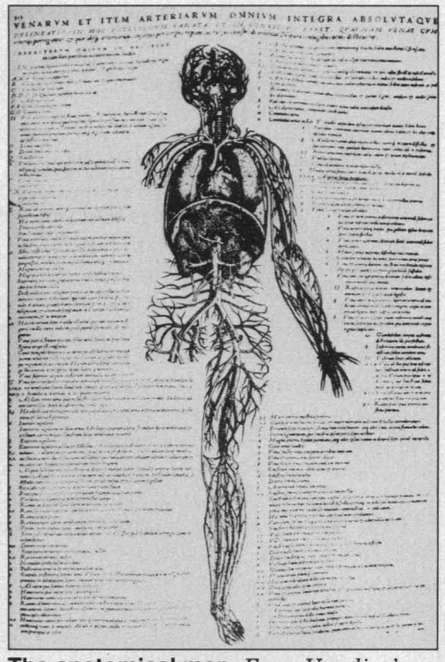
Mapping Terra Incognita (Humani Corporis)

Since the Renaissance, human anatomy has been mapped in ever finer detail—now the genome project



The anatomical map. *From Vesalius'* De Humani Corporis Fabrica, *1543.*

"SINCE THE TIME OF VESALIUS, ANATOMISTS and physiologists have been charting the internal features of the body with ever increasing precision and finer detail," says Victor A. McKusick of Johns Hopkins University who was until recently head of the international Human Genome Organization. Andreas Vesalius' s *De Humani Corporis Fabrica*, he says, is a core text—an opus that laid the intellectual foundation of medicine in the 1500s.

"We've depended on maps to guide medical theory ever since," says McKusick. "We have now arrived at a sort of 'last frontier' of anatomy—that of the human genome."

Today, genes are being mapped to one of the 46 chromosomes at the rate of about a dozen a week, thanks to the tools of molecular genetics. McKusick is willing to bet that by 2005 the location of every one of the 50,000 to 100,000 human genes (no one knows for sure) will have been found, and the human gene map will be complete.

When the last gene is mapped, a process that began in Vesalius's time will be essentially complete—the anatomy of the body and its genes laid out in fine detail. Although the gene-mapping work is now moving forward with remarkable speed, it has not always been thus. Only in the past couple of years have we become used to the breakneck speed with which fragments of DNA are today being localized.

Mapping is fundamentally a visual process, as pictures from past to present show. (The images on this page and the next are selected from lectures given this summer at the Jackson Laboratory in Bar Harbor, Maine, by McKusick and geneticist Thomas Roderick of the Jackson lab.)

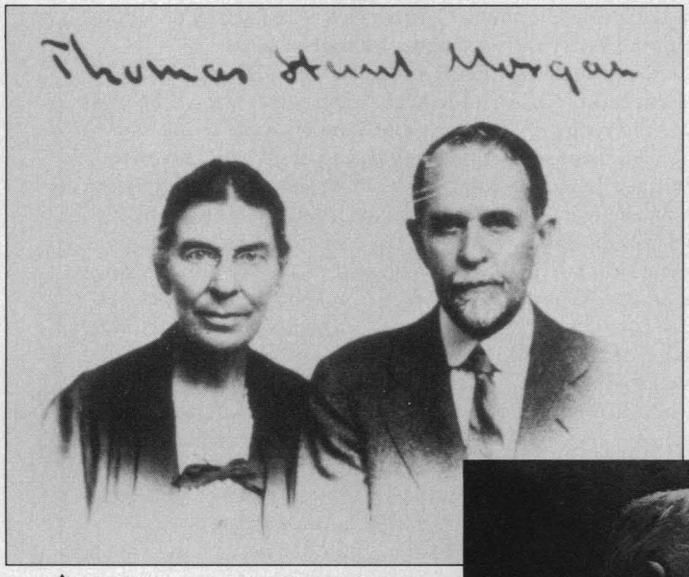
One of the first people in what has become the gene-mapping game was Johann Friedrich Horner, a professor of ophthalmology in Zurich. In 1876 Horner drew a pedigree showing that color blindness runs in families.

A burst of genetic activity followed soon after. "Chromosomes in mitosis were first visualized in tumor cells in 1877 by Walther Flemming of Kiel, Germany," says McKusick. At about the same time Gregor Mendel's famous study of inheritance in peas, published in 1865 but little noted at the time, was "rediscovered," and Mendel's principles were soon linked to the newly discovered chromosomes.

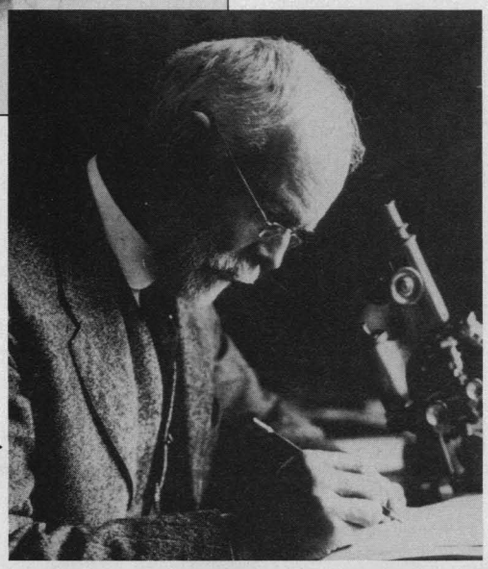
Not too long after that Thomas Hunt Morgan and E. B. Wilson, two newly minted Hopkins Ph.D.'s who had migrated to Columbia, took things a big step further. In 1910, Morgan discovered a male fruit fly with white eyes. They were, he thought, supposed to be red. A series of experiments on several generations of fruit flies, tracing the genetic parentage of white-eyed and red-eyed male and female flies, enabled Morgan to show that the white-eye gene, a recessive, is linked to or carried on the X chromosome, thus establishing the principle of locating genes by "linkage analysis."

Meanwhile Morgan's, colleague E. B. Wilson, was using pedigree studies of human beings to trace inherited traits through generations of the same family. Wilson took Horner's observations a huge step further by mapping the first human gene—for color blindness—to the X chromosome.

Pedigrees have been the heart of gene mapping ever since because for a long time the best way to do genetic studies was to find a genetic abnormality in one individual and then study the family's history to see when and where the gene manifested itself in family members. Finding the

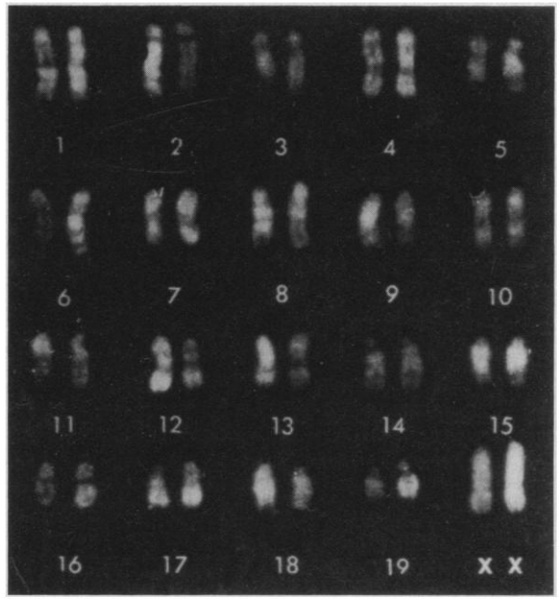


Thomas Hunt Morgan *and his wife in their passport photo for a trip to Stockholm in 1934 when Morgan received the Nobel Prize. Morgan's work with fruit flies is fundamental to modern genetics.*

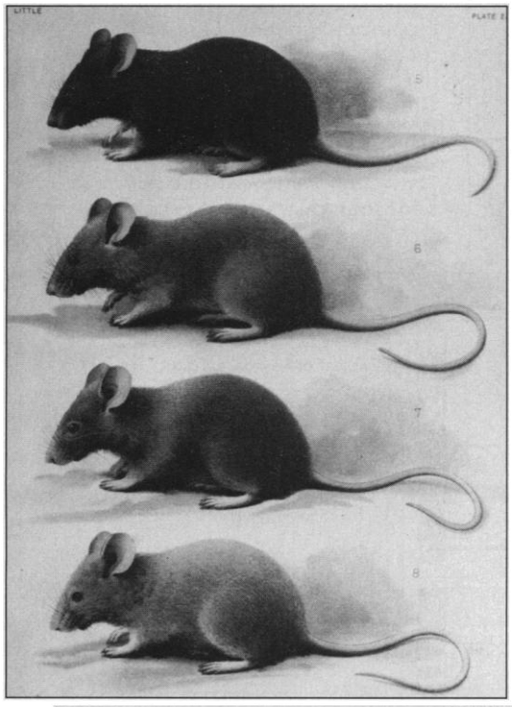


E. B. Wilson, *working at Columbia University, linked color blindness to the X chromosome in 1911.*

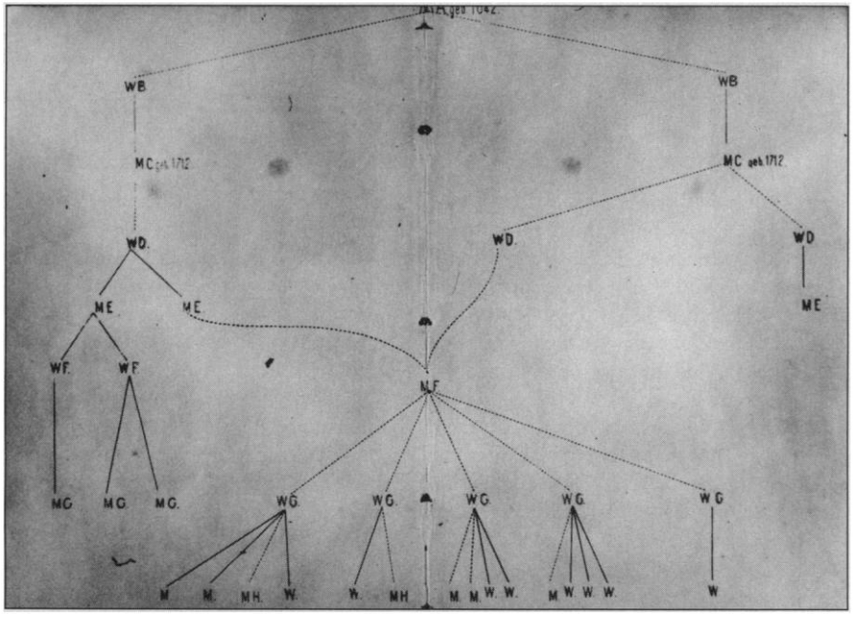
Banding. *Fluorescent banding techniques, available since 1970, reveal the unique identity of every chromosome in the mouse.*



The inbred mouse *has enabled scientists to map 2600 loci in the mouse, whose gene map bears striking homology to the human map.*



Early pedigree. *This pedigree, made by Johann Friedrich Horner, a Zurich ophthalmologist, in 1876, shows that color blindness runs in families.*



genes for cystic fibrosis, Huntington's disease, and other human disorders has depended on pedigree studies, as has the identification of disease genes in the mouse, which serves as an animal model of human disease.

Mouse genetics emerged as a distinct field in the 1950s, largely due to work at the Jackson lab, where inbreeding mice is the *raison d'être.*

As mouse and human gene studies advanced, it became clear that there is phenomenal similarity between the genes of mouse and man and comparative mapping evolved as a specialized field of its own. Data accumulated on substantial similarities between mouse and human chromosomes; some genes for human disease were correctly assigned to a human chromosome only after the corresponding gene was mapped in the mouse.

Roderick, who is coordinating data for the mouse map, believes "the genetic and physical maps of the human genome will move along much quicker and with considerably more meaning if the mouse genome is unraveled simultaneously." Today, the computerized mouse database in Bar Harbor lists 2600 mapped loci (349 are cancer-related genes) and the number is growing exponentially.

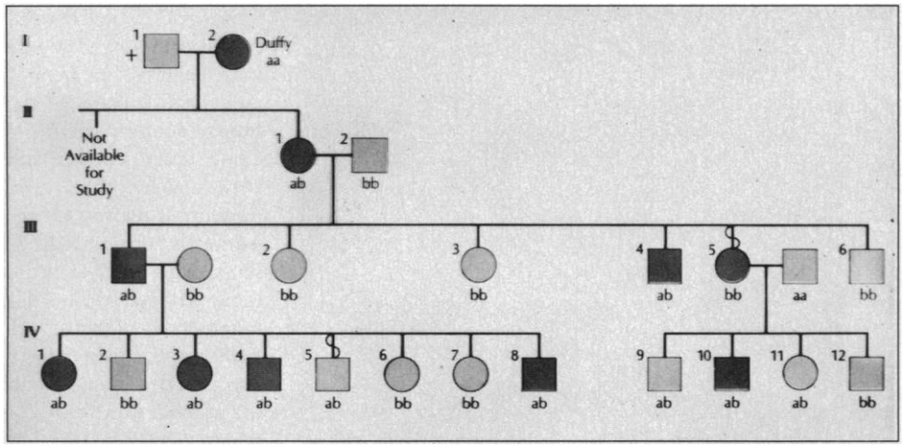
The advent of mouse genetics coincided with the beginning of human medical genetics as we think of it today. Inherited diseases can be identified with biochemical as well as genetic precision, often detected in utero, and, in some cases, they can be treated effectively.

The fact that human beings have 23 pairs of chromosomes—originally thought to be 48—was confirmed in 1956 due to techniques of cytogenetics that enabled researchers to separate chromosomes and lay them out on a page in what is now known as a karyotype. In 1957, during the "era of cytogenetics," the first departments of human medical genetics were founded in the United States—at Hopkins by McKusick and at the University of Washington in Seattle by Arno Motulsky.

Soon after that, McKusick began cataloging inherited disorders with the vague hope that someday science would have the techniques to map each disorder to its gene. In 1966, he published the first volume of *Mendelian Inheritance in Man*—a catalog of 1487 genetic disorders. The ninth edition, published at the beginning of this year, lists 4937 inherited characteristics, with more recorded every week.

By 1968, 68 human genes had been mapped to the X chromosome but none to the other chromosomes: the autosomes that carry information that is not sex-linked. The gap was filled that same year by Roger Donahue, then a Hopkins doctoral student who decided to look at his own chromosomes and discovered that chromosome 1 was much too long. Persuading members of his own family to give him blood for analysis, Donahue found that everyone who had a strung-out chromosome 1 tended to have a particular "Duffy" blood type, thereby showing that the gene for the Duffy blood group is on the first chromosome.

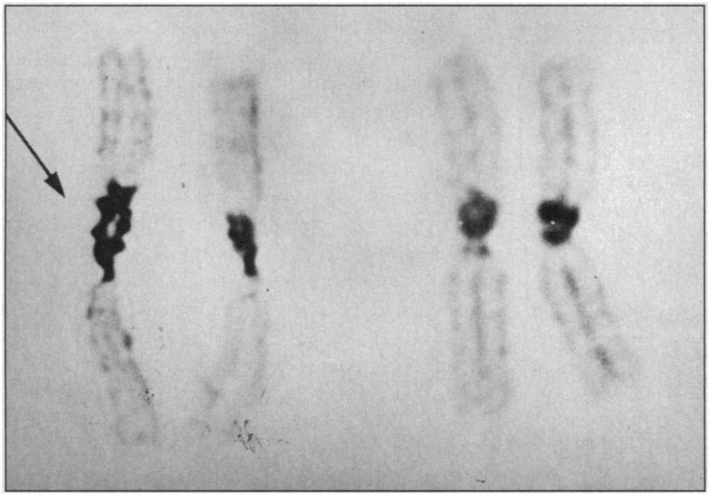
One of the next great strides came a couple of years later when Torbjorn

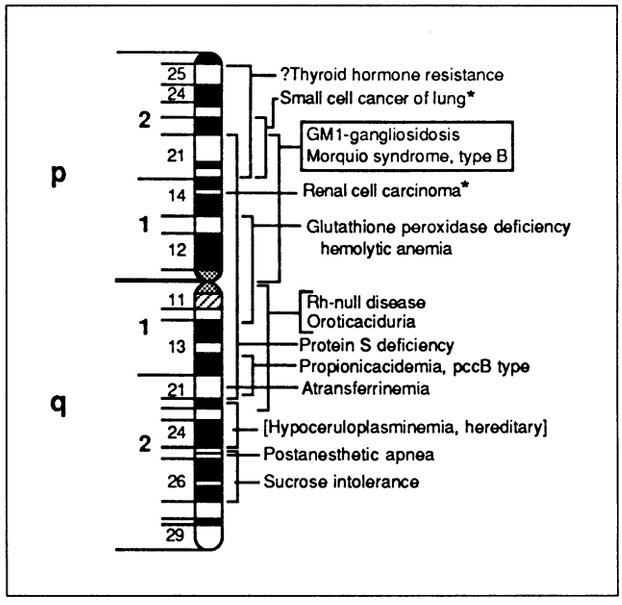


Roger Donahue, *who discovered an unusually long chromosome 1 among family members, used the genetic pedigree to show that the gene for the Duffy blood group is located on chromosome 1. The 1968 discovery was the first assignment of a gene to a chromosome other than the sex-linked X and Y chromosomes.*

Chromosome 3. *The discovery of the gene for small cell cancer of the lung on chromosome 3 was among data from the 1980s that convinced researchers that, in some forms, cancer is a genetic disease.*

Chromosome 1. *An unusually long number 1 chromosome runs in the Donahue family, just the way some families have long noses.*





Caspersson and Lore Zech at the Karolinska Institute in Stockholm developed a technique whereby every one of the 46 human and 40 mouse chromosomes could be identified unambiguously. By staining chromosomes with quinacrine mustard that fluoresced under ultraviolet light, Caspersson and Zech revealed that each chromosome has a unique banding pattern.

Banding was an important discovery. It was complemented in the early 1970s by the discovery of restriction enzymes, which cut DNA in specific places, and by recombinant DNA technology, which made it easier and easier to pluck out a specific stretch of the genetic material. With those methods in hand, mapping became a practical possibility. In 1973 the first workshop devoted exclusively to gene mapping was held at Yale, organized by Frank Ruddle. "At the time," McKusick recalls, "mapping was a recondite effort. Today it is at the very heart of biology and medicine."

For all of the information gleaned over the years about genetic diseases, the idea of mapping every single human gene and, ultimately, deciphering the sequence of its genetic bases, could be nothing more than a scientific daydream until the 1980s when, in a chance encounter at a conference in Alta, Utah, two scientists from opposite sides of the country figured out that "Riflip" technology could be applied to mapping human and mouse genes.

According to a story now beloved by geneticists, David Botstein of the Massachusetts Institute of Technology and Ronald Davis of Stanford were listening to a talk on the importance of locating genes by first identifying them with known markers on a chromosome when it dawned on them that "restriction fragment length polymorphism," or Riflip technology, could give geneticists the wherewithal to find every marker and every gene.

With that, the fine detailed maps of the human and mouse genomes that are now the center of so much scientific excitement became reality and concepts previously believed to be true could be nailed down with molecular precision: among them, cancer as a genetic disease.

McKusick points to chromosome 3 as an example. "Mapping has proved that cancer is a somatic cell genetic disease. With the assignment of small cell lung cancer to chromosome 3, we know that a specificgene is as intimately connected to one form of the disease as are cigarettes."

Today, science is moving down the path initiated by Vesalius at a dizzying pace. Just how fast that pace really is is suggested by a remark at the meeting on Roderick's turf in Bar Harbor. For the gene mapping incrowd, the scorecard of genes mapped from summer to summer is always a highlight at the yearly Bar Harbor meeting, and there were years when a handful of genes was a big score. This year, when McKusick presented the human scorecard—1756 functional genes and more than 2000 DNA segments as of 27 June—he offered his audience an apology for the fact that his slide, some 3 weeks old, was "terribly out of date."

"By today," he said, "I'm sure the number has gone up." As of 10 September, 1884 genes had homes on the map.

■ BARBARA J. CULLITON