A brief history of medical diagnosis and the birth of the clinical laboratory

Part 5a — The foundation of molecular science and genetics

By Carren Bersch, Editor

A t the conclusion of “Fraud and abuse, managed care and lab consolidation” — Part 4 of this series of articles in December 1999 — the author wrote: “Only a few years ago, laboratory visionaries predicted that developments in molecular biology had the potential to change laboratory medicine in the same way that computed tomography and magnetic resonance imaging altered the practice of radiology. Speculation that routine hospital admissions testing done in the 21st century could include a panel of DNA probes in place of a chemistry profile or complete blood cell count now look more plausible than ever. … On the verge of the 21st century, the lab is providing more information about the human condition faster and more accurately than ever. It is strategically positioned for success in the healthcare industry — in the business of supplying critical information in the information age.”

Where do we stand?
It is now 2006, and the future is here. The healthcare industry is burgeoning with new companies that are involved in the molecular “revolution,” many of which have come into being as recently as the completion of the sequencing of the human genome was announced on April 14, 2003. It was at this point that the so-called genetic blueprint of life was available to researchers and scientists who began the continuing mad genomic scramble, this time to identify the approximately 30,000 human genes.

Biomedical research has been driven by the prospect of discovering what genes are involved in diseases as complex as cancer and diabetes. Already, new treatment methods and “designer drugs” — made to suit a particular genetic profile — are being enabled by the sequencing results, as is earlier diagnosis of certain diseases through genetic testing. In the past decade, with the availability of technology and with knowledge fueled by the investment and interest in the Human Genome project, molecular diagnostics has recently enabled laboratories to offer diagnostic and predictive tests for inherited disorders. And while molecular testing seemingly arrived all in a flurry, there is a long history of unglamorous trial-and-error behind today’s movement toward personalized medicine, which involves pharmacogenomics and nutrigenomics.

Mendel to Morgan to modern DNA
The precursor to the current era of molecular genetic testing in humans reaches back 141 years to Gregor Johann Mendel’s 1865 publication of experimental data. Mendel (1822-1884) joined the Augustinian Order of monks in 1843. His experiments with peas in the monastery’s garden led him to formulate the basic principles of heredity. Between 1856 — three years before Charles
Darwin’s *Origin of Species* was published — and 1863, Mendel cultivated and tested some 28,000 pea plants. His experiments brought forth two generalizations which later became known as Mendel’s Laws of Heredity or Mendelian inheritance.

His basic tenets related to the transmission of hereditary characteristics from parent organisms to their children. When Mendel published his theory in 1865, biologists who did not believe his results were especially important largely ignored them. Even Mendel himself believed that his results applied to only certain categories of species and did not thoroughly understand his theory’s applicability.

At the start of the 20th century, Mendel’s work was “rediscovered,” arousing much controversy. Linked in this confused rediscovery, European scientists Hugo de Vries, Carl Correns, and Erich von Tschermak brought Mendel’s early theory of heredity to light. Despite a number of detractors and a few promoters, Mendel’s ideas were eventually merged with Thomas Hunt Morgan’s chromosome theory of inheritance in 1915 and, thus, became the core of classical genetics.3,6

Morgan was an American geneticist and embryologist (1866-1945). He received his bachelor’s degree from the State College of Kentucky (now the University of Kentucky), his PhD from Johns Hopkins University, and at Bryn Mawr worked on embryology during his tenure there. By 1910, following the rediscovery of the Mendelian model in which the chromosomes of cells were thought to hold the actual hereditary particles, Morgan’s research moved to the study of mutation in the fruit fly: *Drosophila melanogaster*. In Morgan’s famous Fly Room at Columbia University, and at Bryn Mawr worked on embryology during his tenure there. By 1910, following the rediscovery of the Mendelian model in which the chromosomes of cells were thought to hold the actual hereditary particles, Morgan’s research moved to the study of mutation in the fruit fly: *Drosophila melanogaster*. In Morgan’s famous Fly Room at Columbia University, he demonstrated that genes are carried on chromosomes and are the mechanical basis of heredity — forming the foundation of modern genetic science and guaranteeing Mendel’s place in scientific history.3,5

**The move toward revealing DNA**

From this point on, many scientists not nearly so famous as Mendel and Morgan labored on with experiments that, one by one, continued to add to the body of knowledge concerning genetics. While Linus Pauling and his colleagues introduced the term “molecular disease” into the medical vocabulary in 1949 (based on their discovery that a single amino acid change at the beta-globin chain leads to sickle-cell anemia), the next big public sensation in the field was the discovery of DNA by Watson and Crick. While the two men did not become household words, the three little letters D-N-A did.

Deoxyribonucleic acid (DNA) was actually isolated in 1869 by Swiss chemist Friedrich Miescher. He later demonstrated that DNA exists only in chromosomes, the site of hereditary material. By the 1930s, DNA was known to be a large molecule in the form of a long chain of nucleotides; but, other than that, its structures and functions were poorly understood. By then, geneticist George Beadle and biochemist Edward Tatum teamed up to investigate the relations between genes and enzymes. In 1943, Oswald Avery had identified the genetic role of DNA: that DNA carried genetic information and might well be the gene.8

**Two teams, two approaches, one answer**

Almost as fascinating as the scientific studies that unfolded from Mendel down to Avery is the tale of how James Dewey Watson and Francis Harry Compton Crick converged at the same time, in the same place and, in 1959, cracked the DNA code. Crick was a Briton who had studied physics, then chemistry and biology, and still had not earned a doctoral degree. At age 19, Watson — an American — had graduated from the University of Chicago and had received his doctorate at age 22. He had studied ornithology but changed career paths when he went to Europe for post-doctoral studies.

Another team — Maurice Hugh Frederick Wilkins and Rosalind Elsie Franklin — were working with DNA at King’s College in London. At a conference in Italy, Watson heard Wilkins speak and was introduced by him to a photograph of a DNA molecule which had been rendered by his colleague, Franklin, via X-ray crystallography. With this bit of knowledge, Watson was immediately keen to solve the riddle of DNA.9

Watson (now 23, became a research fellow at Cambridge) and Crick (now 35, and a graduate student there) had admired the work of Linus Pauling who had discovered in 1948 “that many proteins take the shape of an alpha helix, spiraled like a spring coil.” They were also aware of the stud-

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**Figure 1. History of genetics timeline**

1858 Charles Darwin, Alfred Russel Wallace
Joint announcement of the theory of natural selection: that members of a population who are better adapted to the environment survive and pass on their traits.

1859 Charles Darwin
Published *The Origin of Species*.

1866 Gregor Mendel
Published the results of his investigations of the inheritance of “factors” in pea plants.

1900 Carl Correns, Hugo de Vries, Erich von Tschermak
Mendel’s principles were independently discovered and verified, marking the beginning of modern genetics.

1902 Walter Sutton
Pointed out the inter-relationships between cytology and Mendelism, closing the gap between cell morphology and heredity.

1905 Nettie Stevens, Edmund Wilson
Independently described the behavior of sex chromosomes: XX determines female; XY determines male.

1908 Archibald Garrod
Proposed that some human diseases are due to “inborn errors of metabolism” that result from the lack of a specific enzyme.

1910 Thomas Hunt Morgan
Proposed a theory of sex-linked inheritance for the first mutation discovered in the fruit fly, *Drosophila*, white eye. This was followed by the gene theory, including the principle of linkage.

1927 Hermann J. Muller
Used X-rays to cause artificial gene mutations in *Drosophila*.

1928 Fred Griffith
Proposed that some unknown “principle” had transformed the harmless R strain of *Diplococcus* to the virulent S strain.

1931 Harriet B. Creighton, Barbara McClintock
Demonstrated the cytological proof for crossing-over in maize.

**1941**
George Beadle, Edward Tatum
Irradiated the red bread mold, *Neurospora*, and proved that the gene produces its effect by regulating particular enzymes.

**1944**
Oswald Avery, Colin MacLeod, Maclyn McCarty
Reported that they had purified the transforming principle in Griffith’s experiment and that it was DNA.

**1945**
Max Delbruck
Organized a phage course at Cold Spring Harbor Laboratory which was taught for 26 consecutive years. This course was the training ground of the first two generations of molecular biologists.

**late 1940s**
Barbara McClintock
Developed the hypothesis of transposable elements to explain color variations in corn.

**1950**
Erwin Chargaff
Discovered a one-to-one ratio of adenine to thymine and guanine to cytosine in DNA samples from a variety of organisms.

**1951**
Rosalind Franklin
Obtained sharp X-ray diffraction photographs of DNA.

**1952**
Martha Chase, Alfred Hershey
Used phages in which the protein was labeled with 3S and the DNA with 3P for the final proof that DNA is the molecule of heredity.

**1953**
Francis Crick, James Watson
Solved the three-dimensional structure of the DNA molecule.

**1958**
Matthew Meselson, Frank Stahl
Used isotopes of nitrogen to prove the semiconservative replication of DNA.

**1958**
Arthur Kornberg
Purified DNA polymerase I from *E. coli*, the first enzyme that made DNA in a test tube.

**1966**
Marshall Nirenberg, H. Gobind Khorana
Led teams that cracked the genetic code: that triplet mRNA codons specify each of the twenty amino acids.

**1969**
Likely the first year that DNA replication was determined to be semiconservative.

**1970**
Paul Modrich
Discovered that DNA repair enzymes function by removing mistakes in the DNA.

**1975**
Seymour Benzer
Continued the study of how genetic information is transmitted in bacteria.

**1977**
Lester Rodman
Work on human DNA in the 1970s included the discovery of the first human gene that is silenced in cancer, the *p53* gene.

**1980**
E. F. T. Sanger
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**1983**
Anastasios Karaliopoulos
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**1990**
Kary Mullis
Invented PCR, which has revolutionized molecular biology.

**1995**
James Watson
Discovered that DNA replication is semiconservative.

**1999**
Dan Nocera
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2000**
J. Craig Venter
Continued the study of how genetic information is transmitted in bacteria.

**2003**
Joyce Hirschman
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2004**
John Sulston
Continued the study of how genetic information is transmitted in bacteria.

**2005**
David Baltimore
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2006**
Bruce Stillman
Continued the study of how genetic information is transmitted in bacteria.

**2007**
Michael Rosbash
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2008**
David Enard
Continued the study of how genetic information is transmitted in bacteria.

**2009**
Eric Lander
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2010**
Julian Adams
Continued the study of how genetic information is transmitted in bacteria.

**2011**
Chris Akey
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2012**
Robert Edgar
Continued the study of how genetic information is transmitted in bacteria.

**2013**
Sara Hurwitz
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2014**
David Liu
Continued the study of how genetic information is transmitted in bacteria.

**2015**
Debra Flannery
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2016**
David Gems
Continued the study of how genetic information is transmitted in bacteria.

**2017**
Sara Hurwitz
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2018**
Sara Hurwitz
Continued the study of how genetic information is transmitted in bacteria.

**2019**
Sara Hurwitz
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2020**
Sara Hurwitz
Continued the study of how genetic information is transmitted in bacteria.

**2021**
Sara Hurwitz
Discovered the first human gene that is silenced in cancer, the *p53* gene.

**2022**
Sara Hurwitz
Continued the study of how genetic information is transmitted in bacteria.

**2023**
Sara Hurwitz
Discovered the first human gene that is silenced in cancer, the *p53* gene.
— except for occasional errors, or mutations. They published these findings in *Nature* in 1953; Rosalind Franklin’s findings were published in the same issue as a “supporting article.” Because their model had fit experimental data so well, Watson and Crick’s structure was widely accepted. In 1962, Watson, Crick, and Wilkins won the Nobel Prize for physiology/medicine. Rosalind Franklin had, by this time, died at age 37 of ovarian cancer, and by the conditions required by the Nobel Prize Committee that only living persons be recognized, she could not be one of the recipients.

“The discovery of DNA, the explanation of its construct, has been acknowledged as the most important biological work of the last 100 years, and the field it opened may be the scientific ‘frontier’ for the next 100.” In the 50 years since Watson and Crick revealed their DNA findings, the field of molecular diagnostics has flourished (see Figure 2). The 1985 invention of polymerase chain reaction (PCR) provided the boost that scientists needed to improve their capabilities to diagnose inherited diseases on the DNA level.

“PCR opened the door to eliminating complexities, costs, and time requirements of available technologies like cloning and sequencing. Its ability to generate exponential copies of a target sequence means that a known mutation can be identified within a day rather than months. PCR also eliminated the necessity for radioactivity for routine molecular diagnosis, so that the clinical laboratory is now able to provide genetic services for carrier or population screening for known mutations, as well as prenatal diagnosis of inherited diseases. From PCR, mutation-detection techniques developed can be categorized under enzymatic-based methods, electrophoretic-based methods, and solid phase-based techniques.”

Some of the disease-related gene mutations are recessive (they must be present in both gene copies, one from each parent) before they cause dysfunction, while others are dominant (a single altered gene copy can cause disease). Some are X- or sex-linked, associated with the X or Y chromosome that determines our gender, and are found only in males or females. Some mutations have arisen and been passed down in specific families and some are more prevalent in individuals of certain ethnic descent.

For example, carriers of certain mutations of the BRCA1 or the BRCA2 gene (especially Ashkenazi Jewish women) are at a higher risk of both breast cancer and ovarian cancer, often at an earlier age than the general population. Individuals of Ashkenazi Jewish descent are also at increased risk for inheriting Tay-Sachs, Gaucher, Canavan disease, and Familial Dysautonomia — genetic diseases that can occur when both parents have an abnor-

**Challenges for widespread application of molecular diagnostics**

- Defining the appropriate circumstances for ordering
- Developing therapies that correct or address specific genetic defects or genetic risk factors
- Developing consensus on standards of care
- Educating physicians and patients concerning the potential information from testing
- Providing access to affordable testing and services
- Providing adequate controls to prevent discrimination at work, within communities, and for insurance coverage
- Performing tests on platform technologies that are easy to control
- Developing adequate proficiency testing and consistency among laboratories
- Training a sufficient number of medical technologists to perform highly complex testing
- Interpreting the results in the context of the clinical history and other results
- Integrating results with other family members and ethnicity, while complying with HIPAA
- Providing adequate genetic counseling support for physicians and patients
- Obtaining adequate reimbursement for performing the tests and the potential liability
- Obtaining necessary regulatory approval and coding for reimbursement
- Convincing carriers and payers of the merits of providing payment coverage

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Alec Jeffreys
Coined the term DNA fingerprinting and was the first to use DNA polymorphisms in paternity, immigration, and murder cases.

Francis Collins, Lap-Chee Tsui
Identified the gene coding for the cystic fibrosis transmembrane conductance regulator protein (CFTR) on chromosome 7 that, when mutant, causes cystic fibrosis.

First gene replacement therapy: T cells of a four-year old girl were exposed outside of her body to retroviruses containing an RNA copy of a normal ADA gene. This allowed her immune system to begin functioning.

FlavrSavr tomatoes, genetically engineered for longer shelf life, were marketed.

What is on the molecular diagnostics horizon?
The 21st century is barely underway, and molecular diagnostics is the hottest topic in the clinical laboratory field. Making molecular diagnostics widely available means overcoming obstacles and resolving issues that have surfaced in its development. In the next segment of “A brief history of medical diagnosis and the birth of the clinical laboratory,” Part 5b will detail the most up-to-date testing methods and pertinent automation technologies, and examine the impact these will have on everyday healthcare decisions.

References
3. Kaufman HW, Strom CM. From peapods to labora-

This adapted chart was developed by Jo Ann Lane, a 1994 Woodrow Wilson National Fellowship Foundation’s National Leadership Program for Teachers participant, and is used through the courtesy of WWNFF Leadership Program for Teachers (www.woodrow.org/lpt/LPTnational.php) and Access Excellence @ the National Health Museum (www.accessexcellence.org/AE/AEPC/WWC/1994/geneticstln.html).