

NATIONAL ACADEMY OF SCIENCES

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1915—2006

A Biographical Memoir by
MARY E. CASE AND FREDERICK J. DE SERRES

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Biographical Memoir

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WASHINGTON, D.C.



Norman G. H.

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August 6, 1915–October 16, 2006

BY MARY E. CASE AND FREDERICK J. DE SERRES

NORMAN GILES WAS recognized as a pioneer in the fields of radiation cytology and fungal genetics. His early studies (1939-1955) were on microsporogenesis and chromosome aberrations in *Tradescantia*. His first use of *Neurospora crassa* as an experimental organism was in reversion analyses of inositol mutants. This followed the work of Beadle and Tatum, who dealt with reversion of nutritional mutants. Subsequently, a number of important papers by Giles followed, including contributions on intragenic complementation, gene conversion, and analysis of gene clusters. He made particularly significant contributions to our molecular understanding of regulation of the genes of biochemical pathways in microorganisms, especially *Neurospora crassa*.

Norman was born in Atlanta, Georgia, on August 6, 1915, to Norman H. Giles Sr., a realtor, and Alice Guerard Giles, a registered nurse. Early on, he exhibited an interest in natural history, and at the age of 11, in 1926, he became a charter member of the Georgia Botanical Society. However, his major interest then was in birds, an interest fostered by his mother, who maintained a bird feeder shelf. In 1936 Norman and his birding companion Don Eyles initiated the publication of a quarterly journal devoted to ornithology in Georgia, *The Oriole*. He was a charter member of the

Georgia Ornithological Society, founded in December 1936. At the first biennial meeting of the society, in 1937, *The Oriole* became the official organ of the society. These bird watching and natural history activities would play a predominant role in his life for many years, even after his retirement.

Norman attended public schools along with his younger brother Cuthbert (“Bert”). He then attended Boys’ High School in Atlanta, and upon graduation in 1934 he received a first-year scholarship to Emory University, to which he commuted by streetcar. At Emory he majored in biology, with an emphasis on genetics. It was at Emory that he met his first wife, Dorothy Evelyn Lunsford, who was also a biology major. In later years Dorothy served as one of his research assistants at Oak Ridge and then at Yale, especially in experiments with *Neurospora*.

Upon graduation from Emory with an A.B. degree in biology in 1937, Norman was awarded a Beck Foundation Fellowship. He decided to attend Harvard, entering in the fall of 1937. He married Dorothy Lunsford on August 26, 1939. Later, in 1951 and 1953, they adopted two children: Annette Guerard Giles (later Annette Brown) and David Lunsford Giles.

At Harvard Norman soon came under the influence of the world-renowned cytogeneticist, Karl Sax, the “father” of radiation cytology, and decided to complete his Ph.D. with Sax. At that time Norman was associated with an exceptional group of graduate students in the Biology Department, many of whom were later elected to membership in the National Academy of Sciences: Charles Rick, Carl Swanson, Reed Rollins, Bob Galambos, Donald Griffin, Carol Williams, and Vincent Dethier.

Following graduation Norman remained at Harvard on a Parker Fellowship for a postdoctoral year and performed, at the suggestion of Sax, the classical experiments on the

induction of chromosomal rearrangements in *Tradescantia* microspores by fast neutrons. Norman demonstrated that chromosomal rearrangements, translocations induced in microspores of *Tradescantia paludosa* by fast neutrons, exhibited a linear relationship to dosage (one-hit aberrations). This was in marked contrast to the same rearrangements induced by X rays, which had been shown by Sax to increase as the square of the dose (two-hit aberrations). His later studies with X-ray-induced rearrangements involved analyzing the effects of oxygen in increasing aberration frequencies. One of the most striking results was his demonstration that the effect of oxygen is immediate.

In 1941 Norman accepted his first professional appointment as instructor in botany at Yale, where he remained for the next 30 years. This included a three-year leave of absence from 1947 to 1950, during which he carried out research at the Biology Division of Oak Ridge National Laboratory in Tennessee. At Yale he served as instructor in botany (1941-1945), assistant professor (1945-1946), associate professor (1946-1951), and professor of botany and then professor of biology (1951-1961). His final appointment at Yale was as the Eugene Higgins Professor of Genetics (1961-1972).

Norman spent the summer of 1941 at the Cold Spring Harbor Laboratory on Long Island. There he attended the summer symposium on "Genes and Chromosomes—Structure and Organization," which lasted for several days and provided an opportunity for him to meet a number of seminal figures in genetics, including Demerec, Rhoades, McClintock, Delbruck, Luria, Muller, Wright, and Stadler.

During the fall of his first year at Yale, Norman was very excited by the publication in the *Proceedings of the National Academy of Sciences* of a paper by Beadle and Tatum on biochemical mutants in *Neurospora crassa*. He decided to use *Neurospora* as an experimental organism in his studies of

radiation-induced mutations, especially back mutations. His first paper in this field was coauthored with Ester Lederberg and appeared in 1948.

With respect to research in genetics, the 1940s were an exciting time to be in the Botany Department at Yale. Edward Tatum had just moved to Yale from Stanford and was soon joined by an exceptional graduate student, Joshua Lederberg. Tatum's continuing research on *Neurospora*, especially Lederberg's exciting experiments on mating in bacteria, eventually resulted in the award of Nobel Prizes to Beadle, Tatum, and Lederberg. In addition, there was a second active research group at Yale working with *Neurospora* led by David Bonner, which included Patricia St. Lawrence and Charles Yanofsky.

While on leave from Yale from 1947 to 1950, Norman served as principal biologist in the Biology Division at Oak Ridge National Laboratory. Under the inspiring leadership of Alexander Hollander, a great deal of innovative research was being performed in the division. Norman continued his studies on chromosome rearrangements in *Tradescantia* induced by fast neutrons and X rays and began his research with back mutations (reversions) of inositol mutants in *Neurospora*.

Norman's associates in research at Oak Ridge included Fred J. de Serres, Herbert Parkes Riley, Alvin Beatty, and Alan Conger. During this period, Norman employed one of us (M.E.C.) as a research assistant in experiments performed with *Neurospora*. When he returned to Yale in the fall of 1950, M.E.C. decided to move to New Haven and later enrolled as a graduate student working with Norman. She received her Ph.D. degree in 1957 and became a research associate with Norman, the beginning of a long and mutually fruitful collaboration.

Norman's next area of research involved studies of ultra-violet- and X-ray-induced reversions of inositol mutants of *Neurospora crassa*. He demonstrated that most reversions were the result of back mutations at the same locus, although some resulted from suppressor mutations at other loci. Different mutants altered at the inositol locus exhibited markedly different rates of reverse mutation, and these differences were inherited in a Mendelian fashion. Studies with M.E.C. on allelic recombination at the *pan-2* locus demonstrated for the first time that copy-choice mechanisms could involve several different mutational sites at one locus.

In the early 1950s Norman became interested in utilizing mutations induced by UV and X rays to determine the nature of the mutations blocking various biochemical pathways in *Neurospora*. Complementation studies were used to separate the mutants into those altered in different loci.

Complementation analysis of purple adenine mutants by one of us (F.J.D.) indicated that these mutations could be separated into two very closely linked loci, *ad-3A* and *ad-3B*. These two loci were later found by others to be responsible for two sequential enzymatic steps in adenine biosynthesis. F.J.D. was Norman's first graduate student.

Studies by his graduate students Norma Nelson and Dow Woodward and his research associate C. W. H. Partridge conducted with mutants altered at the *ad-4* locus, which lack adenylosuccinase, provided the first examples of allelic complementation and the first allelic complementation maps. The mechanism of allelic (or interallelic) complementation was revealed much later by others; certain alterations in different regions or domains within the same polypeptide chain can complement each other in multimeric proteins.

Norman's next studies involved extensive genetic and biochemical analyses of what was first interpreted as a complex of five enzymes in the polyaromatic biosynthetic

pathway involving the conversion of DAHP (3-deoxy-D-arabino-heptulosonate-7-phosphate) to ESSP (3-enolpyruvylshikimic acid-5-phosphate). These studies involved characterizing scores of *arom* mutants, including ones shown to be the result of nonsense mutations in the first gene in the cluster, resulting in the loss of the five sequential enzymatic activities. Others later showed that the *arom* region encodes a dimer composed of two pentafunctional polypeptide chains. In the studies of *arom* mutants the absence of one class of mutants in the gene-encoding biosynthetic dehydroquinase was eventually explained by the discovery of two dehydroquinases in *N. crassa*, one constitutive and one inducible. The discovery of the inducible dehydroquinase led to the detection of another complex region in the genome of *N. crassa*, the *qa* gene cluster encoding five structural and two regulatory genes involved in the utilization of quinic acid as a carbon source.

Norman's first wife, Dorothy, died in January 1967, and he married Doris Vos Weaver on August 1, 1969, in the process acquiring two stepdaughters: Gayle Weaver (who died in 1970) and Alix Weaver.

In 1972 Norman accepted an appointment as the Fuller E. Callaway Professor of Genetics at the University of Georgia. Five of his Yale colleagues accompanied him to Georgia: Wyatt Anderson, Bruce Carlton, Mary Case, Ronald Cole, Howard Rines, and Dan Vapnek. At Georgia he established a program in genetics, which in 1980 became the Department of Genetics with Wyatt Anderson as its head. Norman often told his associates at Georgia and elsewhere that Thomas Wolfe was wrong. You can go home again.

Probably the most significant contribution to genetics made by Norman and his collaborators, including his fellow faculty members Sidney Kushner and Daniel Vapnek, was the detailed analysis of the *qa* gene cluster.

These studies eventually led to the cloning and sequencing of the entire cluster of seven genes. They provided early definitive evidence for the expression in *E. coli* of eukaryotic genes. They also provided the first evidence for transformation in *N. crassa* by the expression of *Neurospora* genes carried by hybrid *E. coli* plasmids.

The *qa* cluster was shown to consist of five structural and two regulatory genes located on an 18×10^3 base pair region in a continuous array. The *qa* genes are induced by quinic acid and are coordinately controlled at the transcriptional level by the products of the positive and negative regulatory genes, *qa-1F* and *qa-1S*, respectively, which are transcribed in opposite directions. The *qa-1F*⁺ allele encodes an activator protein required for its own transcription (autoregulation) and for synthesis of the other *qa* mRNAs, including *qa-1F* mRNA. On the other hand, *qa-1S*⁺ encodes a repressor that blocks the activity of the activator and indirectly controls its own expression. The activity of the repressor is inhibited by the inducer quinic acid. The *qa-S*⁻ mutants encode super-repressors insensitive to inducer inhibition, whereas *qa-1S*^C mutants encode inactive repressors. The positive role of *qa-1F* in transcriptional activation is supported by the *in vitro* demonstration of activator binding to 16 base pair target sequences in front of each *qa* gene.

In additional studies the relevant DNA sequences of 23 regulatory mutants were determined from three classes of pleiotropic mutants and were interpreted in terms of functional domains within each regulator. The results are consistent with the roles ascribed to the two regulatory genes in mediating expression of the *qa* cluster. These overall results were summarized in a paper published in the *Journal of Molecular Biology* (1989) with seven of his collaborators: Robert F. Geever, Layne Huiet, James A. Baum, Brett M. Tyler, Virginia B. Patel, Barbara J. Rutledge, and Mary Case.

Norman had an unusual ability to understand the potential of many diverse organisms for genetic research. While he was at Yale, he mentored students who worked not only on *Neurospora* but also on other fungi, such as yeast and *Aspergillus* as well as an alga (*Chlamydomonas*) and moss (*Physcomitrella patens*). This diversity of systems provided a rich educational environment for his students. Many continued these studies successfully in their future careers. For example, Gerald Fink studied histidine biosynthesis in *Saccharomyces cerevisiae* and demonstrated that three enzymatic activities for that pathway are contained on a trifunctional polypeptide chain. The complex contained two identical chains. (Fink was later elected to the National Academy of Sciences).

In addition to these genetic studies, Norman, with Ernest Chu, carried out a series of cytological experiments at Yale involving primate chromosomes. They determined the chromosome number and morphology of several different primate species. In addition, they carried out experiments on the induction of chromosomal aberrations in human cells in tissue cultures.

One of Giles's graduate students at Yale was Karim Abdul El-Eryani from North Yemen. Karim had received his bachelor's and master's degrees from the University of Georgia before deciding to attend Yale for continuing graduate work in genetics. (His stay at the University of Georgia occurred long before Norman decided to move there.) Karim's research at Yale dealt with the genetic control of the biosynthesis of phenylalanine and tyrosine. Karim later became the prime minister of North Yemen.

When Norman and Doris moved to Georgia in 1972, their relocation provided an opportunity to construct a wonderful new home. They had an architect design a very modern house situated on 10 acres of deciduous woodland in a new subdivision named Hanover. Their house was placed above

a rushing stream with a natural waterfall. This site enabled them to continue their interest in gardening in an untouched setting.

Norman's return to Georgia resulted in a renewal of his interest in botany. He reinitiated his work on polyploidy and geographic distribution of species in the genus *Cuthbertia*, a botanically close relative of *Tradescantia* in the southeast. His additional studies established the existence of a new hexaploid complex in *Cuthbertia*. This population occurred in central Florida and resulted from a cross of diploid *C. ornata* with tetraploid *C. graminea* followed by chromosome doubling.

While living in New England, Norman continued his membership in the Georgia Ornithological Society; his return to Georgia permitted an active renewal of bird watching in the southeast. Norman was an inveterate world traveler, having been around the world five times. He visited over 60 countries and all seven continents, including three trips to Antarctica. Many of Norman's trips involved attendance at international genetics meetings or were simply for the joy of traveling.

During Norman's stay at Yale, he took two sabbatical leaves, both supported by Guggenheim fellowships. On his first sabbatical, in 1959, he and his family spent a year in Copenhagen, Denmark, where he carried out research at the Institute of Genetics headed by Mogens Westergaard at the University of Copenhagen. His stay in Copenhagen was also supported by a Fulbright Fellowship. On his second sabbatical in 1965 Norman and his family spent eight months in Canberra, Australia, at the Australian National University in the Laboratory of Genetics headed by David Catchside.

The following excerpt concerning Norman's travels is quoted from a letter from one of his genetics colleagues, David Perkins.

Most appraisals of Norm's impressive career concern laboratory research and academia. There is another facet that is known only to a few of us. His world travels have not been devoted entirely to bird-watching. For two decades, beginning with a visit to China, he was responsible for enriching the collection of wild *Neurospora* strains from exotic places. T. C. Sheng at Fudan University was aware, in 1979, of Norman's interest in sampling wild *Neurospora* populations. Before the revolution, Sheng had used *Neurospora* for his Ph.D. work at Columbia University and as a postdoc at Cal Tech. When he returned to China, first Lysenko genetics and then the cultural revolution made it impossible for him to continue. He retained his interest, however. Following the downfall of the Gang of Four, Sheng made an announcement at the first meeting of the Genetics Society of China, asking members to send him *Neurospora* from their home areas. The responses were generous, ranging from Tibet to Yarbin to Yunnan. How to get the strains out of China was problematic because of official policy about export of natural resources. It was Norm Giles who solved the problem by carrying the cultures with him when he left.

On later trips, Norm was on the lookout for *Neurospora* and was prepared to take his own samples. As a result, the Fungal Genetics Stock Center catalog now lists *Neurospora* strains that he picked up in 1992 from the Caribbean area and from South America, and in 1997 from Pacific islands that lie between Hawaii and Tahiti. A number of the strains are the only samples present from the geographical areas where they were found.

Norman served in many capacities and received numerous honors during his career. He was elected to Phi Beta Kappa and Sigma Xi in his junior year at Emory. Upon graduation he received a Beck Scholarship for further graduate study. Norman was awarded an honorary Sc.D. from Emory in 1980 and an honorary M.A. degree from Yale in 1951.

From 1954 to 1964 Norman served as a consultant to the Atomic Energy Commission. He was a member of the Genetics Study Section at the National Institutes of Health from 1960 to 1964 and a member of the Genetics Training Committee of NIH from 1966 to 1970. He served on the education advisory board of the John Simon Guggenheim Memorial Foundation from 1977 to 1986. He was a member of the editorial boards

of *Radiation Research* from 1953 to 1958, the *American Naturalist* from 1961 to 1964, and *Developmental Genetics* from 1979 to 1986. He served on the Board of Directors of the University of Georgia Research Foundation from 1979 to 1985. He held Fulbright and Guggenheim Fellowships from 1959 to 1960 (while on sabbatical leave from Yale). He received a second Guggenheim fellowship in 1966.

Norman received two awards from the University of Georgia: the Lamar Dodd Award in 1985 for research, and the bicentennial Silver Medallion in 1984. He received the Thomas Hunt Morgan Medal of the Genetics Society of America in 1988. He was elected a fellow of the American Academy of Arts and Sciences and a member of the National Academy of Sciences in 1966. He was chairman of the Genetics Section of the National Academy of Sciences from 1976 to 1979. His membership in the Genetics Society of America included a term as treasurer from 1954 to 1956 and as president in 1970. He also served as president of the American Society of Naturalists in 1977. He was an honorary member of the Genetics Society of Japan and a foreign member of the Royal Danish Academy of Sciences and Letters. He was also an associate of the American Ornithologists' Union for over 70 years.

When Norman retired in 1986, the Department of Genetics established an annual lectureship in his name. The department also conducted a successful fundraising campaign to endow a professorship in his name. The first recipient of the Norman and Doris Giles Professorship in Genetics was Jeffery Bennetzen, who was appointed in 2003. Bennetzen was elected to membership in the National Academy of Sciences in 2004.

Norman Giles died on October 16, 2006, in Manchester, New Hampshire. His wife, Doris, had died in August 2004. He is survived by his daughter, Annette Giles Brown of Nor-

wich, Vermont; his son, David Giles of Jacksonville, Florida; his stepdaughter, Alix Weaver of Northridge, Massachusetts; and his grandson, Dylan Giles Brown of Philadelphia, Pennsylvania.

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