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Abstract

Our recent review included a timeline showing 30 significant events in the history of Neurospora (Davis and Perkins 2002, Nature Reviews Genetics 3:397-403). Many important contributions could not be included in that brief chronology because of space limitations. We present here a somewhat more complete and better documented list of noteworthy developments.

NEUROSPORA CHRONOLOGY - 1843-2002

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Our recent review included a timeline showing 30 significant events in the history of Neurospora (Davis and Perkins 2002, Nature Reviews Genetics 3:397-403). Many important contributions could not be included in that brief chronology because of space limitations. We present here a somewhat more complete and better documented list of noteworthy developments. Publications are cited here only by author and date. Complete references will be found in the books and reviews given at the end of the list.

1843. The first published account of Neurospora (commissioned by the Minister of War) describes material from contaminated bakeries in Paris. Orange pigment is shown to be induced by light. (Payen 1843)
1901. F.A.F.C. Went reports the use of Neurospora (called *Monilia sitophila*) as a component of edible *ontjam* cakes in Java. He uses the orange fungus to examine the effect of substrates on various enzymes. (Went 1901)
1909. *Neurospora* is used in a study of oxidases. (Pringsheim 1909}
1913. *Neurospora* is used in studies of chemical toxicity. (Kunkel 1913, 1914)
1923. Luxuriant growth of Neurospora is seen following the 1923 earthquake and great fire in Tokyo. Perithecia with eight-spored asci are found in the bark of burned trees and are produced on artificial medium. (Kitasima 1924, Kitazima 1925)
1924. The orange pigment is identified as a carotenoid. (Tokugawa and Emoto 1924)
1927. The genus is named, species are described, and B. O. Dodge initiates genetic and cytological studies. Shot asci are used to show 4:4 segregation of mating type genes. Ascospores are shown to be activated by heat. (Shear and Dodge 1927)
1927. A cytological study reveals how ascus development in *N. tetrasperma* is programmed to enclose nuclei of opposite-mating-type in each of the four heterokaryotic ascospores. (Dodge 1927)
1928. T. H. Morgan takes Neurospora cultures with him when moving from Columbia University to establish the Biology Division at the California Institute of Technology. (See Lindegren 1973)
1928. Carl Lindegren selects *N. crassa* as the preferred species for genetics and proceeds to develop stocks and obtain markers. (Lindegren 1931, 1933; See Lindegren 1973)
1935. *N. intermedia* is described as a new species. (Tai 1935)
1935. Ascospore activation is examined physiologically. (Goddard 1935, 1939)
1936. The first genetic map is published, consisting of six loci. (Lindegren 1936)
1939. Neurospora is used as a textbook example showing first and second division segregation in the linear ascus, with crossing over at the four-chromatid stage. (Sturtevant and Beadle 1939; Sinnott and Dunn 1939, Waddington 1939)
1941. Beadle and Tatum use Neurospora to obtain the first biochemical mutants. (Beadle and Tatum 1941)
1943. 'Race tubes' are used to measure linear growth rate on agar media and to determine optimal conditions for growth. (Ryan *et al.* 1943)
1943, 1946. Conditional biochemical mutants are identified. (Stokes *et al.* 1943, Mitchell and Houlahan 1946)
1944. Mutants are identified that affect different steps in the same biosynthetic pathway. (Srb and Horowitz 1944)
1944. Heterokaryons are studied systematically using mutant markers. (Beadle and Coonradt 1944)
1944-45. Strains of opposite mating type are shown to be heterokaryon-incompatible. (Beadle and Coonradt 1944, Sansome 1945)
1945. Barbara McClintock identifies the seven chromosomes, describes meiosis and postmeiotic mitoses, and identifies a translocation. (McClintock 1945)
1947. The first suppressor of a biochemical mutation is discovered. (Houlahan and Mitchell 1947)
1947. A synthetic medium is devised for making crosses. (Westergaard and Mitchell 1947)
1948. Ascospores are shown to be activated by furfural . (M. B. Emerson 1948)
1948. Enzyme activity is shown to be absent in cell-free extracts of a *trp-3* mutant. (Mitchell and Lein 1948)
1948. Sorbose is used to obtain colonial growth. (Tatum *et al.* 1948)
1948, 53. Chromosome cytology and behavior in the ascus are described and documented in detail. (Singleton 1948, 1953)
1948, 53, 67. Genetic linkage groups are assigned to cytologically defined chromosomes. (Singleton 1948, St. Lawrence 1953, Barry 1967)
1949. Linkage data are presented that establish six linkage groups. (Houlahan *et al.* 1949)
1949-54. Accumulated evidence makes it increasingly clear that genes specifying different steps in the same biosynthetic pathway are not clustered. (Houlahan *et al.* 1949, Barratt *et al.* 1954)
1950. Temperature sensitive mutants are cited in support of the one gene-one enzyme hypothesis. (Horowitz and Leupold 1951)
1950. A simplified method for preserving cultures by lyophilization is described. (Barratt and Tatum 1950)
1951. Neurospora is found growing in large patches in areas devastated by a volcanic eruption in New Guinea. (Burges and Chalmers 1952)

1952-53. The first maternally transmitted nonmendelian mutants are described. (M. B. and H. K. Mitchell 1952; M. B. Mitchell *et al.* 1953)
1953. Individual heterokaryon-incompatibility (*het*) genes are identified, that block heterokaryon formation when alleles are different. (Garnjobst 1953)
1953. Heterokaryons are used to recover recessive lethal mutations. (Atwood and Mukai 1953)
1953. Different alleles are shown to produce forms of an enzyme with qualitatively different properties. (Horowitz and Fling 1953)
1953-54. A filtration-enrichment method is used to obtain mutants. (V.Woodward 1953, Catcheside 1954)
1954. Genetic maps are constructed for all seven linkage groups and data are compiled for all the known markers. Genetic nomenclature is adopted using Drosophila as a model. (Barratt *et al.* 1954)
1955. Cross-reacting material related to the wild-type enzyme is demonstrated immunologically in an auxotrophic mutant. (Suskind *et al.* 1955)
1955. Mary Mitchell uses ascus analysis to provide the first definitive proof of gene conversion. (Mitchell 1955)
1956. Translational suppression is analyzed at the molecular level. (Yanofsky 1956)
1956. A formula is devised that allows minimal medium to be made up and stored conveniently in 50 strength solution. (Vogel 1956)
1957-59. Complementation between allelic mutations is shown, first for heterokaryons, then for protein products *in vitro*. (Fincham and Pateman 1957, Giles *et al.* 1957, D. Woodward 1959)
1957-59. Insertional translocations are identified and shown to generate partial-diploid progeny that are duplicated for the displaced segment. (de Serres 1957, St. Lawrence 1959)
1959. Rhythmic conidiation is shown to be under circadian control. (Pittendrigh *et al.* 1959)
1959. Enrichment for new mutants is accomplished by the method of 'inositol-less death': When an inositol-requiring single-mutant strain is incubated in minimal medium, unbalanced growth results in rapid death unless a new, second mutation has occurred.. (Lester and Gross 1959)
1960. Ejected groups of eight ascospores are used extensively for unordered tetrad analysis. (Strickland 1960)
1960. Microconidia are used to determine a haploid DNA content of ~45 megabases. (Horowitz and Macleod 1960)
1960. The Fungal Genetics Stock Center is established, directed by Raymond Barratt.
1960-62. Polyphosphate metabolism is described. (Harold 1966 review)
1961. Ninety-three workers attend the first Neurospora Information Conference. (*NAS-NRC Publication* 950, 1962)
1961. Intragenic recombination is shown to be polarized. (Murray 1961, 1963)
1962. Meiotic crossing over and interference in a multiply marked Neurospora chromosome is shown to resemble that of Drosophila and maize. (Perkins 1962)
1962. *Neurospora Newsletter* begins publication, edited by Barbara Bachmann..
1962. Methods are developed for studying forward and reverse mutation in the *ad-3* region, and heterokaryons are used to recover recessive mutations. (de Serres and Osterbind 1962)
1962. Drug-resistant mutants are characterized and mapped. (Hsu 1962, 1963, Howe and Terry 1962)
1962. A method is described for preserving cultures in suspended animation on anhydrous silica gel. (Perkins 1962).
1962-69. Homothallic Neurospora species are described. (Gochenaur and Backus 1962, Frederick *et al.* 1969)
1964. Mitochondrial DNA is isolated and characterized. (Luck and Reich 1964)
1964. '*rec*' genes are shown to control meiotic recombination differently in local regions. (Catcheside *et al.* 1964)
1965. Coordinate control of unlinked genes in the same biosynthetic pathway is described. (Gross 1965)
1965. Cross-pathway ('general') control of amino acid synthesis is discovered. (Carsiotis and Lacy 1965)
1965. *Neurospora Bibliography and Index* (Yale University Press) is published, listing 2310 publications that deal with Neurospora. (Bachmann and Strickland 1965)
1966-74. Patterns of ascospore abortion in unordered asci are used to detect and characterize chromosome rearrangements. Insertional and terminal rearrangements are used to map genes by duplication coverage. (Perkins 1966, 1974)
1967. Metabolic cross-suppression is described between intermediates in arginine and pyrimidine synthesis. (Davis 1967, Reissig *et al.* 1967)
1967. A terminal pericentric inversion is identified and used to show that unstable partial diploid progeny are generated; these are inhibited because they are heterozygous for the heterokaryon-incompatible mating type genes *mat A* and *mat a*. (Newmeyer and Taylor 1967)
1967. Resetting the circadian clock is shown to be mediated by a blue-light photoreceptor. (Sargent and Briggs 1967)
1968. Positive control is demonstrated in the regulation of sulfur metabolism. (Marzluf and Metzenberg 1968)
1968. Systematic sampling is begun of wild Neurospora populations. (Perkins *et al.* 1976).
1970. Radiation-sensitive mutations are obtained, including some that impair meiotic recombination. (Schroeder 1970)
1970. Microelectrode techniques indicate existence of a proton pump in the cell membrane. (Slayman and Slayman 1970)
1970. The *tol* mutation is discovered and shown to suppress mating type-associated heterokaryon incompatibility in *N. crassa*. (Newmeyer 1970)
1970. A compilation is published of genetic and microbiological methods. (Davis and de Serres 1970)
1971. Enzymes specific to different biosynthetic pathways are shown to be channelled in separate pools. (Williams *et al.* 1971)

Glyoxysomal enzymes are localized. (Flavell and Woodward 1971)
The genes that control quinate catabolism are shown to be clustered. (Chaleff 1972, 1974)
1972. Evidence is obtained that DNA from Neurospora mitochondria is circular. (Clayton and Brambl 1972)
1972, 1979. The synaptonemal complex karyotype is reconstructed from thin sections and the distribution of recombination nodules is described. (Gillies 1972, 1979)
1973. Mutants are isolated that alter the period length of circadian conidiation. (Feldman and Hoyle 1973).
1973. Compartmentation within the cell is demonstrated for the enzymes and intermediates of arginine metabolism. (Weiss and Davis 1973, Weiss 1973)
1973. DNA-induced changes are reported that are attributed to transformation. (Mishra and Tatum 1973)
1975. A complete 452-residue amino acid sequence is obtained for NADP-specific glutamate dehydrogenase, specified by the *am* gene (Holder *et al.* 1975)
1975. Allozymes are used to show that genetic polymorphisms are abundant in natural populations of *N. intermedia*. (Spieth 1975)
1975-76. The expression of heterokaryon incompatibility differences in partial diploids enables known *het* loci to be defined and mapped and reveals the presence of previously unrecognized *het* loci in nature. *het* genes are shown to be polymorphic in a wild population. (Perkins 1975, Mylyk 1975, 1976).
1976-77. The plasma-membrane ATPase is characterized. (Scarborough 1976, Bowman and Slayman 1977)
1976. A biological species concept is adopted for the genus Neurospora. Fertility tests with standard testers are used to assign wild-collected strains to species. (Perkins *et al.* 1976)
1976-79. Spore-killer factors that resemble meiotic drive elements in Drosophila and mouse are discovered in natural populations of *N. intermedia* and *N. sitophila*. (Turner and Perkins 1979)
1977. Biosynthesis of aromatic amino acids (and PABA) is shown to be controlled by a 'cluster gene' with a single protein product containing segments that specify five separate enzymatic activies. (Gaertner and Cole 1977)
1977. A review of Neurospora cytogenetics includes information on 170 mapped chromosome rearrangements. (Perkins and Barry 1977)
1978. *N. crassa* mitochondrial DNA is sequenced. (Heckman *et al.* 1978)
1978, 1982. Mutant mating type alleles are obtained. (Griffiths and DeLange 1978, Griffiths 1982)
1979. Effective methods are developed for transformation. (Case *et al.* 1979)
1979. 5S RNA genes are shown to be dispersed as single copies. (Free *et al.* 1979)
1979-84. Heterokaryons are employed in a system developed for genome-wide detection of recessive lethal mutation. This is used in quantitative studies to demonstrate induced repair of genetic damage and to measure a dose-rate effect on recovery of mutations. (Stadler and Crane 1979, Stadler and Moyer 1981, Stadler and Macleod 1984)
1980. Codon usage is shown to be modified in Neurospora mitochondria. (Heckman *et al.* 1980)
1980. Select photographs of meiosis and ascus development are published. (Raju 1980)
1980. Honeybees are observed gathering Neurospora conidia as though they were pollen. (Shaw and Robertson 1980)
1980-84. Vacuoles are purified (Cramer *et al.* 1980; Vaughn and Davis 1981) and their functions characterized. (Cramer and Davis 1984)
1981. The first mitochondrial plasmid is discovered. (Collins *et al.* 1981)
1982. A comprehensive compendium is published, with descriptions of ~500 chromosomal loci and genetic maps of the seven linkage groups. (Perkins *et al.* 1982)
1982. Physical and genetic maps of the mitochondrial genome are published. (Collins *et al.* 1982, O'Brien 1992)
1982. The novel V-type ATPase is discovered. (E.J. and B. J. Bowman 1982)
1982-83. The *am* gene is cloned and the DNA sequence obtained. (Kinnaird *et al.* 1982, Kinnaird and Fincham 1983)
1982. A maternally transmitted senescence factor is discovered in *N. intermedia* strains from Hawaii. (Rieck *et al.* 1982, Griffiths and Bertrand 1984)
1983. Trichogynes are shown to respond to mating-type-specific pheromones. (Bistis 1983)
1983. Membrane potentials and resistances are measured using inserted microcapillary electrodes. (Blatt and Slayman 1983)
1984. An efficient method is devised for RFLP mapping of cloned DNA segments. The dispersed 5S RNA genes are mapped using the method. (Metzenberg *et al.* 1984, 1985)
1985-86. DNA libraries are prepared in plasmids, cosmids, and phage lambda. (Akins and Lambowitz 1985, Vollmer and Yanofsky 1986, Orbach *et al.* 1986)
1985. Recessive diplophase-lethal or -detrimental genes are shown to be abundant in wild-collected strains of the heterothallic species *N. crassa*. (Leslie and Raju 1985)
1985-92. Genes are identified that have greatly elevated expression levels during conidiation. (Berlin and Yanofsky 1985, Sachs and Yanofsky 1991, Springer *et al.* 1992)
1986. *N. discreta* is described as a new heterothallic species. (Perkins and Raju 1986)
1986. The *Neurospora Information Conference* becomes *Fungal Genetics Conference*. The *Neurospora Newsletter* becomes *Fungal Genetics Newsletter*.
1987. Genes in duplicated DNA segments are shown to be mutated premeiotically. The process is called RIP (Repeat Induced Point-mutation). (Selker *et al.* 1987)
1987. Telomeres are cloned.and shown to have the same DNA sequence as that of human telomeres. (Schechtman 1987, 1990)
1987-89. Restriction endonucleaase sites in mitochondrial and nuclear DNAs are used to determine phylogenetic relationships of

Neurospora species and to test validity of the biological species concept. (Natvig *et al.* 1987, Taylor and Natvig 1989; see Spukski *et al.* 1997)
1988. Mating type genes are cloned, sequenced, and shown to be present as single copies. Because *mat A* and *mat a* are nonhomologous, they are called *idiomorphs* rather than alleles. (Glass *et al.* 1988)
1988. Pulsed field gel electrophoresis is used to separate whole-chromosome DNAs and provide an elecrophoretic karyotype. (Orbach *et al.* 1988)
1989. The *Tad* retrotransposon is discovered in a strain from Africa. (Kinsey and Helber 1989)
1989. The first clock-controlled genes are identified. (Loros *et al.* 1989)
1989. Scanning EM is used to study conidiation in the wild type and in mutants. (Springer and Yanofsky 1989)
1989. Mitochondrial plasmids are shown to be transferred horizontally. (May and Taylor 1989)
1989-93. Premeiotic changes in the number of ribosomal DNA repeats are shown to occur in the nucleolus organizer region. (Butler and Metzenberg 1989, 1990, 1993)
1990. Serial reconstruction from elecron micrographs of thin sections reveals the occurrence of synaptic adjustment at pachytene in the pairing loops of inversion heterozygotes. (Bojko 1990)
1990. The *Tad* retrotransposon is shown to be transmitted from one nucleus to another in heterokaryons. (Kinsey 1990).
1991, 1995. Analysis of a new UV-sensitive mutant reveals a novel excision-repair DNA endonuclease. (Ishii *et al.* 1991, Yajima *et al.* 1995)
1992. Genes in duplicated DNA segments are shown to undergo epigenetic silencing ('quelling') in vegetative cells. (Pandit and Russo 1992, Romano and Macino 1992)
1992. Wild type *N. tetrasperma*, which normally exists as a *mat A* + *mat a* heterokaryon, is shown to carry a nonfunctional allele of the *tol* gene. (Jacobson 1992)
1994. Autoregulation of the circadian clock gene *frq* is shown to involve negative feedback. (Aronson *et al.* 1994)
1994. Abnormal colony morphology in *ropy* mutants is shown to reflect defects in a molecular-motor protein that is required for normal nuclear distribution. (Plamann *et al.* 1994)
1994. Proof is provided for a polyprotein precursor of two enzymes. (Gessert *et al.* 1994)
1994, 1998. Centromeric DNA is cloned and shown to contain repeats and degenerate transposons. (Centola and Carbon 1994, Cambareri *et al.* 1998)
1995. A novel Neurospora kinesin (N-kinesin) is discovered. (Steinberg and Schliwa 1995)
1996. Genes in unpaired DNA segments are shown to be inactivated during meiosis. (Aramayo and Metzenberg 1996).
1996. The *mat A* idiomorph is shown to consist of three genes, while *mat a* is a single gene. (Ferreira *et al.* 1996)
1996 Alleles of the vegetative incompatibility gene *het-c* are cloned and sequenced (Saupe *et al.* 1996)
The life history of *N. intermedia* is studied in a natural setting. (Pandit and Maheshwari 1996
Furfural released from burned sugar cane is implicated in the activation of ascospores in the soil. (Pandit and Maheshwari 1996)
1997. Cumulative information is published on 355 chromosome rearrangements. (Perkins 1997)
1997. Trans-specific polymorphisms are shown for vegetative incompatibility alleles. (Saupe and Glass 1997)
1997. The thymidine kinase gene from herpes virus is introduced and expressed in Neurospora. (Sachs *et al.* 1997)
1997-99. Quelling-deficient mutants are obtained and used to show that vegetative-phase gene silencing requires an RNA-dependent RNA polymerase. (Cogoni and Macino 1997, 1999)
1997-2000. Expressed sequences (ESTs) from different developmental stages are used to identify cDNAs (Nelson *et al.* 1997, Dolan *et al.* 2000)
1998. Genome sequencing of Linkage Groups II and V (>1/3 of the genome) is initiated in Germany. (*http://www.mips.biochem.mpg.de/proj/Neurospora*)
1998. Mutants deficient in DNA-methylation are obtained. (Foss *et al.* 1998)
1999. A gene is identified that encodes an archaeal-like rhodopsin. (Bieszke *et al.* 1999).
2000. The book *Neurospora: Contributions of a Model Organism* describes 60 years of research. (Davis 2000)
2000. The Whitehead Institute receives a National Science Foundation grant of $5.25 million to sequence the entire Neurospora genome. (*NSF News Release, September 26*).
2000-01. Neurospora is found growing under the bark of fire-killed trees at many sites in western North America, and as far north as Fairbanks, Alaska. (Jacobson *et al.* 2001)
2001. *The Neurospora Compendium: Chromosomal Loci* is published, with genetic maps and a description of ~1000 loci. (Perkins *et al.* 2001)
2001. Genome Sequence Assembly Version 1 is released in February by the Whitehead Institute. In October, Version 2 includes alignment of physical and genetic maps. (*www-genome.wi.mit.edu*)
2001. Silencing of unpaired genes during meiosis is shown to require a gene that specifies an RNA-dependent RNA polymerase. (Shiu *et al.* 2001)
2001. DNA methylation is shown to depend on the presence of a functional histone H3 methyltransferase. (Tamaru and Selker 2001)
2001. Methodology is described for obtaining good expression of Green Fluorescent Protein in Neurospora. (Freitag *et al.* 2001)
2002. Inactivation of genes by RIP is shown to require a DNA methyltransferase-like protein. (Freitag *et al.* 2002).
2002. New versions of the genome sequencing projects are released in Germany and the United States, reporting progress with assembly

and annotation:
http://www-enome.wi.mit.edu/annotation/fungi/Neurospora/
http://www.mips.biochem.mpg.de/proj/Neurospora/
http://pedant.gsf.de/cgi-bin/wwwfly.pl?Set=Neurospora_crassa&Page=index

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