Timeline of Genomics (1951–1976)*

Year	Event and Theoretical Implication/Extension	Reference
1951	**Esther M. Lederberg** discovers bacteriophage lambda, the first viral episome of *E. coli.*	Lederberg, E.M. 1951. Lysogenicity in *E. coli* K12. *Genetics* 36: 560.
1952	**Alfred Day Hershey** (1969 Noble Prize Laureate for Physiology or Medicine) and **Martha Chase** perform an experiment by using T2 bacteriophage that confirms DNA not protein as the genetic material.	Hershey, A.D. and Chase, M. 1952. Independent functions of viral protein and nucleic acid in growth of bacteriophage. *J. Gen. Physiol.* 36: 39-56.
	Jean Brachet suggests that RNA also plays a part in the synthesis of proteins.	Brachet, J., *et al.* 1952. Une étude comparative du pouvoir inducteur en implantation et en microinjection des acides nucléiques et des constituants cellulaires nucléoprotéiques. *Arch. Biol.* 63: 429-440.
	Joshua Lederberg (1958 Noble Prize Laureate for Physiology or Medicine) and **Norton David Zinder** describe transduction, or transfer of genetic information in *Salmonella typhimurium.*	Zinder, N.D. and Lederberg, J. 1952. Genetic exchange in *Salmonella. J. Bacteriol.* 64: 679-699.
	Renato Dulbecco (1975 Nobel Prize Laureate for Physiology or Medicine) shows that single particles of an animal virus can produce areas of cellular lysis called plaques.	Dulbecco, R. 1952. Production of plaques in monolayer tissue cultures by single particles of an animal virus. *Proc. Natl. Acad. Sci. USA* 38: 747-752.
	Salvador Edward Luria (1969 Noble Prize Laureate for Physiology or Medicine) and **Mary Human**, and independently **Jean Weigle,** describe a nongenetic host-controlled modification system in bacteriophage that leads to the study of bacterial systems of restriction and modification, and ultimately the discovery of restriction endonucleases.	1. Luria, S.E. and Human, M.L. 1952. A nonhereditary, host-induced variation of bacteria viruses. *J. Bacteriol.* 64: 557-569. 2. Bertani, G. and Weigle, J.J. 1953. Host controlled variation in bacterial viruses. *J. Bacteriol.* 65: 113-121.
	William Hayes proposes that bacterial conjugation involves the unidirectional transfer of genes from a donor to a recipient cell. Until then, most microbiologists believed that there was either a fusion of cells or an exchange of genetic information. Contemporaneous with **Luca Cavalli-Sforza, Joshua Lederberg,** and **Esther M. Lederberg**, he also shows that a fertility factor, F, a non-chromosomal plasmid, is present only in donor cells.	1. Hayes, W. 1952. Recombination in *Bact. coli* K-12: unidirectional transfer of genetic material. *Nature* 169: 118-119. 2. Lederberg, J., Cavalli, L.L., and Lederberg, E.M. 1952. Sex compatibility in *Escherichia coli. Genetics* 37: 720-730.
	Joshua Lederberg and **Esther M. Lederberg** invent the replica plating technique and provide firm evidence that mutations in bacteria yielding resistance to antibiotics and viruses are not induced by the presence of selective agents.	Lederberg, J. and Lederberg, E.M. 1952. Replica plating and indirect selection of bacterial mutants. *J. Bacteriol.* 63: 399-406.
	Joshua Lederberg uses the term **PLASMID** to describe extranuclear genetic elements that replicate autonomously.	Lederberg, J. 1952. Cell genetics and hereditary symbiosis. *Physiol. Rev.* 32: 403-430.

* Edited by the Editorial Office of *Genomics, Proteomics* & *Bioinformatics.*

Year	Event and Theoretical Implication/Extension	Reference
1953	**Rosalind Elsie Franklin** indicates that DNA is a symmetrical molecule and probably a helix by X ray diffraction study.	1. Franklin, R.E. and Gosling, R.G. 1953. The structure of sodium thymonucleate fibres: I. The influence of water content. II. The cylindrically symmetrical Patterson function. *Acta Crystallographica* 6: 673-677, 678-685. 2. Franklin, R.E. and Gosling, R.G. 1953. Evidence for a 2-chain helix in the crystalline structure of sodium deoxyribonucleate. *Nature* 172: 156-157.
	James Dewey Watson and **Francis Harry Compton Crick** (both are 1962 Noble Prize Laureates for Physiology or Medicine) describe the molecular structure of DNA, propose DNA to be a double-strand helix of nucleotides.	1. Watson, J.D. and Crick, F.H.C. 1953. Molecular structure of nucleic acids: a structure for deoxyribonucleic acid. *Nature* 171: 737-738. 2. Watson, J.D. and Crick, F.H.C. 1953. Genetic implications of the structure of deoxyribonucleic acid. *Nature* 171: 964-967.
	Frederick Sanger (1958 Noble Prize Laureate for Chemistry) and his colleagues work out the complete amino acid sequence for the protein hormone insulin, and show that it contains two polypeptide chains held together by disulfide bridges.	1. Sanger, F. and Tuppy, H. 1951. The amino-acid sequence in the phenylalanyl chain of insulin. I. The identification of lower peptides from partial hydrolysates. *Biochem. J.* 49: 463-481. 2. Sanger, F. and Tuppy, H. 1951. The amino-acid sequence in the phenylalanyl chain of insulin. II. The investigation of peptides from enzymic hydrolysates. *Biochem. J.* 49: 481-490. 3. Sanger, F. and Thompson, E.O. 1953. The amino-acid sequence in the glycyl chain of insulin. I. The identification of lower peptides from partial hydrolysates. *Biochem. J.* 53: 353-366. 4. Sanger, F. and Thompson, E.O. 1953. The amino-acid sequence in the glycyl chain of insulin. II. The investigation of peptides from enzymic hydrolysates. *Biochem. J.* 53: 366-374. 5. Sanger, F. 1959. Chemistry of insulin: determination of the structure of insulin opens the way to greater understanding of life processes. *Science* 129: 1340-1344. 6. Sanger, F. 1960. Chemistry of insulin. *Br. Med. Bull.* 16: 183-188.
1954	**Paul Charles Zamecnik** and his colleagues discover that ribonucleoprotein particles, later named ribosomes, are the site of protein synthesis.	1. Keller, E.B., Zamecnik, P.C., and Loftfield, R.B. 1954. The role of microsomes in the incorporation of amino acids into proteins. *J. Histochem. Cytochem.* 2: 378-386. 2. Littlefield, J.W., Keller, E.B., Gross, J., and Zamecnik, P.C. 1955. Studies on cytoplasmic ribonucleoprotein particles from the liver of the rat. *J. Biol. Chem.* 217: 111-123.

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1954	**George Gamow** proposes the hypothesis of heretical coden.	Gamow, G. 1954. Possible relation between deoxyribonucleic acid and protein structures. *Nature* 173: 318.
1955	**Severo Ochoa** (1959 Noble Prize Laureate for Physiology or Medicine) and **Marianne Grunberg-Manago** discover the first RNA polymerase, polynucleotide phosphorylase.	1. Grunberg-Manago, M., Oritz, P.J., and Ochoa, S. 1955. Enzymatic synthesis of nucleic acidlike polynucleotides. *Science* 122: 907-910. 2. Grunberg-Manago, M., Ortiz, P.J., and Ochoa, S. 1956. Enzymic synthesis of polynucleotides. I. Polynucleotide phosphorylase of *Azotobacter vinelandii. Biochim. Biophys. Acta.* 20: 269-285. 3. Brummond, D.O., Staehelin, M., and Ochoa, S. 1957. Enzymatic synthesis of polynucleotides. II. Distribution of polynucleotide phosphorylase. *J. Biol. Chem.* 225: 835-849. 4. Ochoa, S. 1957. Enzymic synthesis of polynucleotides. III. Phosphorolysis of natural and synthetic ribopolynucleotides. *Arch. Biochem. Biophys.* 69: 119-129.
	Seymour Benzer works out the fine structure of the rII region of phage T4 of *E. coli*, and coins the terms **CISTRON**, **RECON**, and **MUTON.**	Benzer, S. 1955. Fine structure of a genetic region in bacteriophage. *Proc. Natl. Acad. Sci. USA* 41: 344-354.
1956	**Arthur Kornberg** (1959 Noble Prize Laureate for Physiology or Medicine) crystallizes DNA polymerase, the enzyme required for synthesizing DNA.	1. Bessman, M.J., Kornberg, A., Lehman, I.R., Simms, E.S. 1956. Enzymic synthesis of deoxyribonucleic acid. *Biochim Biophys. Acta.* 21: 197-198. 2. Lehman, I.R., *et al.* 1958. Enzymatic synthesis of deoxyribonucleic acid. I. Preparation of substrates and partial purification of an enzyme from *Escherichia coli. J. Biol. Chem.* 233: 163-170. 3. Bessman, M.J., *et al.* 1958. Enzymatic synthesis of deoxyribonucleic acid. II. General properties of the reaction. *J. Biol. Chem.* 233: 171-177. 4. Kornberg, A. 1974. *DNA Synthesis.* Freeman, San Francisco, United States.
	Christian Boehmer Anfinsen (1972 Noble Prize Laureate for Chemistry) concludes that the three-dimensional conformation of proteins is specified by their amino acid sequence.	1. Anfinsen, C.B. and Redfield, R.R. 1956. Protein structure in relation to function and biosynthesis. *Adv. Protein Chem.* 48: 1-100. 2. Redfield, R.R. and Anfinsen, C.B. 1956. The structure of ribonuclease. II. The preparation, separation, and relative alignment of large enzymatically produced fragments. *J. Biol. Chem.* 221: 385-404.
	Joe Hin Tjio and **Albert Levan** revised Walther Flemming's 1898 estimate of the human chromosome count from 24 pairs to 23 pairs.	Tijo, J.H. and Levan, A. 1956. The chromosome number in man. *Hereditas* 42: 1-6.

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1956	**D. L. D. Caspar** and **Rosalind Franklin** independently show the location of the ribonucleic acid within the protein capsid in tobacco mosaic virus.	1. Caspar, D.L.D. 1956. Radial density distribution in the tobacco mosaic virus particle. *Nature* 177: 928. 2. Franklin, R. 1956. Location of the ribonucleic acid in the tobacco mosaic virus particle. *Nature* 177: 929.
	Gerhard Schramm and **Alfred Gierer** show that RNA from tobacco mosaic virus is infectious and by itself can cause the disease and result in new viral particles.	Gierer, A. and G. Schramm. 1956. Infectivity of ribonucleic acid from tobacco mosaic virus. *Nature* 177: 702-702.
	Vernon Martin Ingram reports that normal and sickle-cell hemoglobin differ by a single amino acid substitution.	Ingram, V.M. 1956. Specific chemical difference between the globins of normal human and sickle-cell anemia haemoglobin. *Nature* 178: 792-794.
1957	**Francois Jacob** (1965 Noble Prize Laureate for Physiology or Medicine) and **Elie Wollman** provide evidence of the circular nature of the chromosome in *E. coli* after analyzing data from interrupted mating experiments.	Wollman, E. and Jacob, F. 1957. Sur les processus de conjugaison et de reconbinaison chez *Escherichia coli*. *Ann. Inst. Pasteur* 93: 323-339.
	Heinz Fraenkel-Conrat show that the genetic material of tobacco mosaic virus was RNA.	Fraenkel-Conrat, H. and Williams, R.C. 1957. Virus reconstitution: combination of protein and nucleic acid from different strains. *Biochim. Biophys. Acta.* 24: 87.
	Paul Charles Zamecnik, **Mahlon Bush Hoagland**, and **Mary L. Stephenson** isolate transfer RNA and postulate its function.	Zamecnik, P.C., Hoagland, M.B., and Stephenson, M.L. 1957. Observations on the role of RNA in protein synthesis. In *Cellular Biology: Nucleic Acids and Viruses*. Vol. 5, pp. 273-274. New York Academy of Sciences, New York, USA.
	Seymour Benzer shows that recombination can occur between mutations in the same gene and that genes consist of linear arrays of subunits that can be altered.	Benzer, S. 1957. The elementary units of heredity. In *The Chemical Basis of Heredity* (eds. McElroy, W.D. and Glass, B.), pp. 70-93. Johns Hopkins Press, Baltimore, United States.
1958	**Francis Crick** works out the "central dogma", explaining how DNA functions to make protein. The "sequence hypothesis" posits that the DNA sequence specifies the amino acid sequence in a protein. He also suggests that genetic information flows only in one direction, from DNA to messenger RNA to protein, the central concept of the central dogma.	1. Crick, F. 1958. On protein synthesis. *Symp. Soc. Exp. Biol.* 12: 138-163. 2. Crick, F. 1970. Central dogma of molecular biology. *Nature* 227: 561-563.
	John Cowdery Kendrew (1962 Noble Prize Laureate for Chemistry) elucidates the three-dimensional structure of myoglobin.	Kendrew, J.C., *et al.* 1958. A three-dimensional model of the myoglobin molecule obtained by x-ray analysis. *Nature* 181: 662-666.
	Matthew Meselson and **Franklin Stahl** use the density gradient equilibrium centrifugation technique to demonstrate the semiconservative distribution of density label during DNA replication in *E. coli*, confirming the prediction of Crick and Watson.	Meselson, M. and Stahl, F. 1958. The replication of DNA in *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* 44: 671-682.

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1958	**Stanford Moore, Darrel H. Spackman**, and **William Howard Stein** devise the automatic amino acid analyzer, which greatly accelerated the analysis of proteins.	Moore, S., Spackman, D.H., and Stein, W.H. 1958. Automatic recording apparatus for use in the chromatography of amino acids. *Fed. Proc.* 17: 1107-1115.
1959	**Arthur Pardee, Francois Jacob,** and **Jacque Monod** (1965 Noble Prize Laureate for Physiology or Medicine) show that the enzyme beta-galactosidase is induced by changes in culture conditions. This is the first example of negative control of induction and is due to the action of a repressor protein. It sets the stage for other experiments aimed at further delineating the interaction of a regulatory protein with a site on DNA to control the expression of other genes.	Pardee, A., Jacob, F., and Monod, J. 1959. The genetic control and cytoplasmic expression of "inducibility" in the synthesis of beta-galactosidase by *E. coli. J. Mol. Biol.* 1: 165.
	Jerome Lejeune, Marthe Gautier, and **Raymond Turpin** show that Down's syndrome is a chromosomal aberration involving trisomy of a small telocentric chromosome.	Lejeune, J., Gautier, M., and Turpin, R. 1959. Etude des chromosomes somatiques de neuf enfants mongoliens. *Compt. Rendu. Acad. Sci.* 248: 1721-1722.
	O. Sawada and others demonstrate that antibiotic resistance can be transferred between *Shigella* strains and *Escherichia coli* strains by extrachromosomal plasmids, without involving either transformation or transduction.	Ochiai, K., Yamanaka, T., Kimura, K., and Sawada, O. 1959. *Nippon lji.* 1861: 34.
	Robert L. Sinsheimer demonstrates that bacteriophage phiX174 of *E. coli* contains a single-stranded DNA molecule.	Sinsheimer, R.L. 1959. A single-stranded DNA from bacteriophage phiX174. *Brookhaven Symp Biol.* 12: 27-34.
1960	**Francois Jacob**, **David Perrin**, **Carmen Sanchez,** and **Jacques Monod** propose the **OPERON** concept for control of bacteria gene action. Jacob and Monod later propose that a protein repressor blocks RNA synthesis of a specific set of genes, the lac operon, unless an inducer, lactose, binds to the repressor.	1. Jacob, F., Perrin, D., Sanchez, C., and Monod, J. 1960. L'operon: groupe de genes a l'expression coordonne par un operateur. *Compt. Rendu. Acad. Sci.* 245: 1727-1729. 2. Jacob, F. and Monod, J. 1961. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.* 3: 318-356.
	C. H. Werner Hirs, Stanford Moore, and **William H. Stein** (the latter two are 1972 Noble Prize Laureates for Chemistry) determine the amino acid sequence of ribonuclease.	Hirs, C.H., Moore, S., and Stein, W.H. 1960. The sequence of the amino acid residues in performic acid-oxidized ribonuclease. *J. Biol. Chem.* 235: 633-647.
	Max Perutz (1962 Noble Prize Laureate for Chemistry) elucidated the three-dimensional structure of hemoglobin.	Perutz, M.F. 1960. Structure of hemoglobin. *Brookhaven Symp. Biol.* 13: 165-183.
1961	**Mary Lyon** discovers X-chromosome inactivation.	Lyon, M.F. 1961. Gene action in the X chromosome of the mouse (*Mus musculus* L.). *Nature* 190: 372-373.
	Sydney Brenner (2002 Noble Prize Laureate for Physiology or Medicine), **Francois Jacob,** and **Matthew Meselson** use phage infected bacteria to show that ribosomes are the site of protein synthesis and confirm the existence of a messenger RNA (**mRNA**).	Brenner, S., Jacob, F., and Meselson, M. 1961. An unstable intermediate carrying information from genes to ribosomes for protein synthesis. *Nature* 190: 576-581.

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1961	**Francis Crick**, **Sydney Brenner** and colleagues propose that DNA code is written in "words" (called **CODONS**) formed of three DNA bases. They also propose that a particular set of RNA molecules, subsequently called transfer RNAs (**tRNAs**), act to "decode" the DNA.	Crick, H.F.C., Barnett, L., Brenner, S., and Watts-Tobin, R.J. 1961. General nature of genetic code for proteins. *Nature* 192: 1227-1232.
	Benjamin D. Hall and **Sol Speigleman** show that singled stranded T2 phage DNA can form a hybrid with RNA from T2 infected *Escherichia coli*, thus demonstrating the potential of DNA-RNA hybridization methods.	Hall, B.D. and Speigelman, S. 1961. Sequence complemetarity of T2-DNA and T2-specific RNA. *Proc. Natl. Acad. Sci. USA* 47: 137-146.
	Marshall W. Nirenberg (1968 Noble Prize Laureate for Physiology or Medicine) and **Heinrich J. Matthaei** translate the first genetic codon UUU for phenylalanine. This is the start of successful efforts to decipher the genetic code.	Nirenberg, M.W. and Matthaei, H.J. 1961. The dependence of cell-free protein synthesis in *E. coli* upon naturally occurring or synthetic polyribonucleotides. *Proc. Natl. Acad. Sci. USA* 47: 1589.
1962	**Daniel Nathans** (1978 Noble Prize Laureate for Physiology or Medicine), **Norton Zinder**, and colleagues use *E. coli* cell-free system together with bacteriophage f2 RNA to produce viral coat protein identical in amino acid sequence to that isolated directly from the virus.	Nathans, D., Notani, G., Schwartz, J.H., and Zinder, N.D. 1962. Biosynthesis of the coat protein of coliphage f2 by *E. coli* extracts. *Proc. Natl. Acad. Sci. USA* 48: 1424-1431.
	Werner Arber (1978 Noble Prize Laureate for Physiology or Medicine) proves that a kind of restriction endonuclease existing in body to cut DNA unmethylized.	1. Arber, W. 1962. Biological specificities of desoxyribonucleic acid. *Pathol. Microbiol.* 25: 668-681. 2. Arber, W. and Dussoix, D. 1962. Host specificity of DNA produced by *E. coli.* I. Host controlled modification of phage lambda. *J. Mol. Biol.* 5: 18-36. 3. Dussoix, D. and Arber, W. 1962. Host specificity of DNA produced by *E. coli.* II. Control over acceptance of DNA from infecting phage lambda. *J. Mol. Biol.* 5: 37-49.
	Arthur Kornberg synthesizes DNA *in vitro*, showing that DNA polymerase will produce new strands using precursors, an energy source and a template DNA molecule.	Swartz, M.N., Trautner, T.A., and Kornberg, A. 1962. Enzymatic synthesis of deoxyribonucleic acid. XI. Further studies on nearest neighbor base sequences in deoxyribonucleic acids. *J. Biol. Chem.* 237: 1961-1967.
1963	**James Watson** finds that RNA needs for translation.	Watson, J.D. 1963. Involvement of RNA in the synthesis of proteins. *Science* 140: 17-26.
	Marshall Nirenberg, Heinrich Matthaei, and **Severo Ochoa** show that a sequence of three nucleotide bases (a codon) determines each of 20 amino acids, and finally "cracked" the genetic code.	1. Nirenberg, M., *et al.* 1963. Approximation of genetic code via cell-free protein synthesis directed by template RNA. *Fed. Proc.* 22: 55-61. 2. Nirenberg, M., *et al.* 1966. The RNA code and protein synthesis. *Cold Spring Harbor Symp. Quant. Biol.* 31: 11-24.

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1963	**Brian John McCarthy** and **Ellis T. Bolton** describes a method for quantitative determination of the extent of hybridization of DNA or RNA from different biological sources. By this means, it is possible to determine the extent of sequence homology in the genomes of the organisms.	1. MaCarthy, B.J. and Bolton, E.T. 1963. An approach to the measurement of genetic relatedness among organisms. *Proc. Natl. Acad. Sci. USA* 50: 156-164. 2. Hoyer, B.H., McCarthy, B.J., and Bolton, E.T. 1964. A molecular approach in the systematics of higher organisms. DNA interactions provide a basis for detecting common polynucleotide sequences among diverse organisms. *Science* 144: 959-967.
1964	**Charles Yanofsky** and colleagues establish that gene sequences and protein sequences are colinear: changes in DNA sequence can produce changes in protein sequence at corresponding positions.	Yanofsky, C., *et al.* 1964. On the colinearity of gene structure and protein structure. *Proc. Nat. Acad. Sci. USA* 51: 266-274.
	Robin Holliday proposes that genetic recombination in yeast proceeds through two single stranded breaks made simultaneously at the same sites on the two DNA molecules to be recombined.	Holliday, R. 1964. A mechanism for gene conversion in fungi. *Gen. Res.* 5: 282-304.
	R. Bruce Merrifield (1984 Noble Prize Laureate for Chemistry) invents the solid-phase method for peptide synthesis.	1. Merrifield, R.B. 1964. Solid-phase peptide synthesis. 3. An improved synthesis of bradykinin. *Biochemistry* 14: 1385-1390. 2. Merrifield, R.B. 1965. Automated synthesis of peptides. *Science* 150: 178-185.
1965	**Robert William Holley** (1968 Noble Prize Laureate for Physiology or Medicine) completes determining the sequence of 77 nucleotides in yeast alanine tRNA.	1. Holley, R.W., *et al.* 1965. Structure of a ribonucleic acid. *Science* 147: 1462-1465. 2. Holley, R.W., *et al.* 1965. Nucleotide sequences in the yeast alanine transfer ribonucleic acid. *J. Biol. Chem.* 240: 2122-2128.
	Sol Spiegelman and **Ichiro Haruna** discover an enzyme that allows RNA molecules to duplicate themselves.	Spiegelman, S., *et al.* 1965. The synthesis of a self-propagating and infectious nucleic acid with a purified enzyme. *Proc. Natl. Acad. Sci. USA* 54: 919.
	Sydney Brenner and colleagues characterize the codons used as stop signals in DNA code.	Brenner, S., *et al.* 1965. Genetic code: the "nonsense" triplets for chain termination and their suppression. *Nature* 206: 994-998.
	Ellis Englesberg and colleagues show that an activator protein is required for the expression of the genes determining arabinose metabolism in *E. coli.*	Englesberg, E., *et al.* 1965. Positive control of enzyme synthesis by gene C in the L-arabinose system. *J. Bacteriol.* 90: 946-957.
	Chinese Scientists first complete the synthesis of crystalline bovine insulin.	1. Du, Y.C., *et al.* 1961. Resynthesis of insulin from its glycyl and phenylalanyl chains. *Sci. Sin.* 10: 84-104. 2. Kung, Y.T., *et al.* 1965. Total synthesis of crystalline bovine insulin. *Sci. Sin.* 14: 1710-1716. 3. Kung, Y.T., *et al.* 1966. Total synthesis of crystalline insulin. *Sci. Sin.* 15: 544-561.

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1966	**Jonathan R. Beckwith** and **Ethan R. Signer** transpose the lac region of *E. coli* into another microorganism to demonstrate genetic control.	1. Beckwith, J.R., Signer, E.R., and Epstein, W. 1966. Transposition of the lac region of *E. coli. Cold Spring Harb. Symp. Quant. Biol.* 31: 393-401. 2. Beckwith, J.R. and Signer, E.R. 1966. Transposition of the lac region of *Escherichia coli.* I. Inversion of the lac operon and transduction of lac by phi80. *J. Mol. Biol.* 19: 254-265. 3. Fox, C.F., Beckwith, J.R., Epstein, W., and Signer, E.R. Transposition of the lac region of *Escherichia coli.* II. On the role of thiogalactoside transacetylase in lactose metabolism. *J. Mol. Biol.* 19: 576-579.
1967	**Werner Arber** and colleagues show that bacterial cells contain highly specific enzymes that add methyl groups to adenosine and cytosine at recognition sites.	1. Arber, W. and Kehnlein, U. 1967. Mutational loss of the B-specific restriction in bacteriophage fd. *Pathol. Microbiol.* 30: 946-952. 2. Arber, W. and Linn, S. 1969. DNA modification and restriction. *Annu. Rev. Biochem.* 38: 467-500.
	Waclaw Szybalski and **William C. Summers** show that only one DNA strand (the sense strand) acts as a template for RNA synthesis. They use the technique of DNA-RNA hybridization to anneal the newly synthesized RNA to a parent DNA strand.	1. Summers, W.C. and Szybalski, W. 1967. Y-irradiation of deoxyribonucleic acid in dilute solutions: I. A sensitive method for detection of single-strand breaks of polydisperse DNA samples (bacteriophage, *Sarcina lutea, Escherichia coli, Bacillus subtilis, Crytophaga johnsoni*). *J. Mol. Biol.* 26: 107-123. 2. Summers, W.C. and Szybalski, W. 1967. Gamma-irradiation of deoxyribonucleic acid in dilute solutions: II. Molecular mechanisms responsible for inactivation of phage, its transfecting DNA, and bacterial transforming activity. *J. Mol. Biol.* 26: 227-235.
	Walter Gilbert and **Mark Ptashne** isolate the lac repressor regulatory protein and the lambda repressor protein from bacteriophage respectively.	1. Gilbert, W. and Muller-Hill, B. 1966. Isolation of the lac repressor. *Proc. Natl. Acad. Sci. USA* 56: 1891-1898. 2. Ptashne, M. 1967. Isolation of the phage repressor. *Proc. Natl. Acad. Sci. USA* 57: 306-313. 3. Ptashne, M. 1967. *A Genetic Switch–Phage and Higher Organisms.* Blackwell Publishers, Oxford, United Kingdom.
	Thomas Brock identifies the thermophile bacterium *Thermus aquaticus* from which heat stable DNA polymerase is later isolated and used in the polymerase chain reaction. Isolation and culture of this organism later leads to the discovery of the domain Archea.	1. Brock, T.D. 1967. Micro-organisms adapted to high temperatures. *Nature* 214: 882-885. 2. Brock, T.D. 1967. Life at high temperatures. *Science* 158: 1012-1019.

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1967	**Martin Gellert** and coworkers isolates DNA ligase from *E. coli.*	1. Gellert, M. 1967. Formation of covalent circles of lambda DNA by *E. coli* extracts. *Proc. Natl Acad. Sci. USA* 57: 148-155. 2. Zimmerman, S.B., Little, J.W., Oshinsky, C.K., and Gellert, M. 1967. Enzymatic joining of DNA strands: a novel reaction of diphosphopyridine nucleotide. *Proc. Natl Acad. Sci. USA* 57: 1841-1848. 3. Little, J.W., Zimmerman, S.B., Oshinsky, C.K., and Gellert, M. 1967. Enzymatic joining of DNA strands. II. An enzyme-adenylate intermediate in the dyp-dependent DNA ligase reaction. *Proc. Natl Acad. Sci. USA* 58: 2004-2011.
	Theodor O. Diener discovers viroids, plant viruses that do not have a protein capsid. The infectious agent is a low molecular weight RNA that contains no protein capsid.	Diener, T.O. and Raymer, W.B. 1967. Potato spindle-tuber virus: a plant virus with properties of free nucleic acid. *Science* 158: 378-381.
	R. John Collier describes the mechanism by which diphtheria toxin inhibits protein synthesis in a cell-free system from recticulocytes. This is the first definition at the molecular level of the function of a bacterial protein virulence factor.	Collier, R.J. 1967. Effect of diphtheria toxin on protein synthesis: inactivation of one of the transfer factors. *J. Mol. Biol.* 25: 83-89.
	Mary Weiss and **Howard Green** employ somatic cell hybridization to advance human gene mapping.	Weiss, M.G. and Green, H. 1967. Human-mouse hybrid cell lines containing partial complements of human chromosomes and functioning human genes. *Proc. Natl Acad. Sci. USA* 58: 1104-1111.
1968	**Charles Helmstetter** and **Stephen Cooper**, using the "baby machine", establish the rules for replication in the *Escherichia coli* cell cycle.	Cooper, S. and Helmstetter, C. 1968. Chromosome replication and the division cycle of *Escherichia coli* B/r. *J. Mol. Biol.* 31: 519-540.
	R. Okazaki finds the discontinuous synthesis of the lagging strand during DNA replication, which is later called Okazaki fragment.	Okazaki, R., *et al.* 1968. Mechanism of DNA chain growth. I. Possible discontinuity and unusual secondary structure of newly synthesized chains. *Proc. Natl. Acad. Sci. USA*. 59: 598-605.
	Roy Britten and **Dave Kohne** discover repeating sequences in genome.	Britten, R.J. and Kohne, D.E. 1968. Repeated sequences in DNA. Hundreds of thousands of copies of DNA sequences have been incorporated into the genomes of higher organisms. *Science* 161: 529-540.
1969	**Don J. Brenner** and colleagues establish a more reliable basis for the classification of clinical isolates among members of the Enterobacteriaceae. They use nucleic acid reassociation in which denatured DNA-labelled DNA fragments of one organism are reacted under annealing conditions with DNA of another organism. Studies on many species have proven the value of DNA-DNA hybridization to define a species.	Brenner, D.J., *et al.* 1969. Polynucleotide sequence relationships among members of the Enteriobactiaceae. *J. Bacteriol.* 98: 637-650.

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1969	**Gerald M. Edelman** and **Rodney R. Porter** (both are 1972 Noble Prize Laureates for Physiology or Medicine) independently elucidate the structure of gamma globulin.	1. Edelman, G.M., *et al.* 1969. The covalent structure of an entire gammaG immunoglobulin molecule. *Proc. Natl. Acad. Sci. USA* 63: 78-85. 2. Fruchter, R.G., Jackson, S.A., Mole, L.E., and Porter, R.R. 1970. Sequence studies of the Fd section of the heavy chain of rabbit immunoglobulin G. *Biochem. J.* 116: 249-259. 3. O'Donnell, I.J., Frangione, B., and Porter, R.R. 1969. The disulphide bonds of the heavy chain of rabbit immunoglobulin G. *Biochem. J.* 116: 261-268.
	Jonathan Beckwith first separates a bacterial gene.	Schwartz, D.O. and Beckwith, J.R. 1969. Mutagens which cause deletions in *Escherichia coli*. *Genetics* 61: 371-376.
1970	**Howard Temin** and **David Baltimore** (both are 1975 Noble Prize Laureates for Physiology or Medicine) independently discover reverse transcriptase, an enzyme that makes DNA from an RNA template; enzymatic isolation of DNA will become important for genetic engineering.	1. Temin, H.M. and Mizutani, S. 1970. RNA-dependent DNA polymerase in virions of *Rous sarcoma* virus. *Nature* 226: 1211-1213. 2. Baltimore, D. 1970. Viral RNA-dependent DNA polymerase. *Nature* 226: 1209-1211.
	Hamilton Smith (1978 Noble Prize Laureate for Physiology or Medicine) and **Kent Wilcox** isolate the first restriction enzyme, *Hind*II, a protein that cuts DNA at specific sites defined by the base sequence.	Smith, H.O. and Wilcox, K.W. 1970. A restriction enzyme from *Haemophilus influenzae*: I. Purification and general properties. *J. Mol. Biol.* 51: 379-391.
1971	**Ray Wu** and **Ellen Taylor** deduce the sequence of 12 bases at the ends of the genome of the bacterial virus lambda.	1. Wu, R. 1970. Nucleotide sequence analysis of DNA. I. Partial sequence of the cohesive ends of bacteriophage lamda and 186 DNA. *J. Mol. Biol.* 51: 501-521. 2. Wu, R. and Taylor, E. 1971. Nucleotide sequence analysis of DNA. II. Complete nucleotide sequence of the cohesive ends of bacteriophage lambda DNA. *J. Mol. Biol.* 57: 491-511.
1972	**Paul Berg** (1980 Noble Prize Laureate for Chemistry) creates the first recombinant DNA molecule.	Jackson, D.A., Symons, R.H., and Berg, P. 1972. Biochemical method for inserting new genetic information into DNA of Simian Virus 40: circular SV40 DNA molecules containing lambda phage genes and the galactose operon of *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* 69: 2904-2909.
	Janet Mertz and **Ronald Davis** confirm that the *Eco*R1 cuts DNA at a specific site four to six nucleotides long and yields cohesive ends. This opens the way for cloning.	Mertz, J.E. and Davis, R.W. 1972. Cleavage of DNA by R1 restriction endonuclease generates cohesive ends. *Proc. Natl. Acad. Sci USA* 69: 3370-3374.
1973	**Stanley Norman Cohen** (1986 Noble Prize Laureate for Physiology or Medicine) and **Herbert Wayne Boyer** develop recombinant DNA technology, showing that genetically engineered DNA molecules may be cloned in foreign cells.	Cohen, S.N., Chang, A.C.Y., Boyer, H.W., and Helling, R.B. 1973. Construction of biologically functional bacterial plasmids *in vitro*. *Proc. Natl. Acad. Sci. USA* 70: 3240-3244.

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1973	**Dan Nathans**, **George Khoury,** and **Malcolm Martin** use restriction enzymes to produce the first physical map of a DNA molecule for the virus SV40.	1. Adler, S.P. and Nathans, D. 1973. Studies of SV40 DNA: V. Conversion of circular to linear SV40 DNA by restriction endonuclease from *Escherichia coli* B. *Biochim. Biophys. Acta.* 299: 177-188. 2. Khoury, G., Martin, M.A., Lee, T.N., Dana, K.J., and Nathans, D. 1973. A map of simian virus 40 transcription sites expressed in productively infected cells. *J. Mol. Biol.* 78: 377-389.
	George Laver and **Robert Webster** demonstrate that the genomes of influenza virus strains responsible for pandemics possess genome fragments acquired by genome segment reassortment from influenza strains circulating in animals.	Laver, G. and Webster, R.G.. 1973. Studies on the origin of pandemic influenza. III. Evidence implicating duck and equine influenza as possible progenitors of the Hong Kong strain of human influenza. *Virology* 51: 391-393.
	Joseph Sambrook refines DNA electrophoresis by using agarose gel and staining with ethidium bromide.	Sharp, P.A., Sugden, B., and Sambrook, J. 1973. Detection of two restriction endonuclease activities in *Haemophilus parainfluenzae* using analytical agarose—ethidium bromide electrophoresis. *Biochemistry* 12: 3055-3063.
1974	**Jeff Schell** and **Marc Van Montagu** discover that a circular strand of DNA (a plasmid) carried by *Agrobacterium tumefaciens* transforms plant cells into tumor cells.	1. Zaenen, I., Van Larebeke, N., Van Montagu, M., and Schell, J. 1974. Supercoiled circular DNA in crown-gall inducing *Agrobacterium strains*. *J. Mol. Biol.* 86: 109-127. 2. Van Larabeke, N., Engler, G., Holsters, M., Elcacker, S.V.D., Zaenen, I., Schilperoort, R.A., and Schell, J. 1974. Large plasmid in *Agrobacterium tumefaciens* essential for crown gall-inducing ability. *Nature* 252: 169-170.
	David Hogness and **Michael Grunstein** develop colony hybridization, a technique to transfer bacterial colonies to filters, lyse, and fix the DNA. Labeled probes of single stranded DNA, complementary to the fixed DNA, can be applied to determine the identity of the unknown bacterium.	1. Kreigstein, H.J. and Hogness, D.S. 1974. Mechanism of DNA replication in *Drosophila* chromosomes: structure of replication forks and evidence for bidirectionality. *Proc. Natl. Acad. Sci. USA* 71: 135-139. 2. Grunstein, M. and Hogness, D.S. 1975. Colony hybridization: a method for the isolation of cloned DNAs that contain a specific gene. *Proc. Natl. Acad. Sci. USA* 72: 3961-3965.
1975	**Edward Southern** develops a powerful technique for DNA analysis that has been known as Southern blotting.	Southern, E.M. 1975. Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J. Mol. Biol.* 98: 503-517.
	Cesar Milstein and **Georges J. F. Kohler** (both are 1984 Nobel Prize Laureates for Physiology or Medicine) fuse mouse cells together to produce monoclonal antibodies.	Kohler, G. and Milstein, C. 1975. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256: 495-497.

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1975	**C. M. Wei** and **Bernard Moss**, and **Aaron Shatkin** independently show that messenger RNA contains a specific nucleotide cap at its 5′-end that affects correct processing during translation.	1. Wei, C.M. and Moss, B. 1975. Methylated nucleotides block the 5′-terminus of vaccinia virus mRNA. *Proc. Natl. Acad. Sci. USA* 72: 318-322. 2. Furuichi, Y., Morgan, M., Muthukrishnan, S., and Shatkin, A. 1975. Reovirus messsenger RNA contains a methylated blocked 5′-terminal strucure: m7G(5′)ppp(5′)GmpCp. *Proc. Natl. Acad. Sci. USA* 72: 362-367.
	Mary-Claire King and **Allan Wilson** discover regulator genes—genes that control the timing and output of structural genes.	King, M.C. and Wilson, A.C. 1975. Evolution at two levels in humans and chimpanzees. *Science* 188: 107-116.
1976	**J. Michael Bishop** and **Harold E. Varmus** (both are 1989 Noble Prize Laureates for Physiology or Medicine) show that oncogenes appear on animal chromosomes, and alterations in their structure or expression can result in cancerous growth.	1. Stehelin, D., Guntaka, R.V., Varmus, H.E., and Bishop, J.M. 1976. Purification of DNA complementary to nucleotide sequences required for neoplastic transformation of fibroblasts by avian sarcoma viruses. *J. Mol. Biol.* 101: 349-365. 2. Stehelin, D., Varmus, H.E., Bishop, J.M., and Vogt, P.K. 1976. DNA related to the transforming gene(s) of avian sarcoma virus is present in normal avian DNA. *Nature* 260: 170-173.
	Sidney Altman and **Thomas R. Cech** (both are 1989 Noble Prize Laureates for Chemistry) independently show that RNA can serve directly as a catalyst of hydrolytic reaction.	1. Altman, S. 1975. Biosynthesis of transfer RNA in *Escherichia coli*. *Cell* 4: 21-30. 2. Cech, T.R. and Pardue, M.L. 1976. Electron microscopy of DNA crosslinked with trimethylpsorlen: test of the secondary nature of eukaryotic inverted repeat sequences. *Proc. Natl. Acad. Sci. USA* 73: 2644-2648.
	Susumu Tonegawa (1987 Noble Prize Laureate for Physiology or Medicine) first demonstrate somatic recombination in immunoglobulin genes.	Hozumi, N. and Tonegawa, S. 1976. Evidence for somatic rearrangement of immunoglobulin genes coding for variable and constant regions. *Proc. Natl. Acad. Sci. USA* 73: 3628-3632.