	Discovery of the Secrets of Life Timeline: *A Chronological Selection of Discoveries, Publications and Historical Notes Pertaining to the Development of Molecular Biology.*	
Date	***Discovery or Publication***	***References***
1840	Crystals of plant and animal products do not typically occur naturally. F. L. Hünefeld accidentally observes the first protein crystals— those of hemoglobin—in a sample of dried menstrual blood pressed between glass plates. Hunefeld, *Der Chemismus in der thierischen Organisation*, Leipzig: Brockhaus, 1840, 158-63.	Lesk, Protein Structure, 36;Tanford & Reynolds, Nature's Robots, 22.; Judson, 489
1847	In his dissertation Louis Pasteur begins a series of "investigations into the relation between optical activity, crystalline structure, and chemical composition in organic compounds, particularly tartaric and paratartaric acids. This work focused attention on the relationship between optical activity and life, and provided much inspiration and several of the most important techniques for an entirely new approach to the study of chemical structure and composition. In essence, Pasteur opened the way to a consideration of the disposition of atoms in space." (DSB) Pasteur, *Thèses de Physique et de Chimie, Presentées à la Faculté des Sciences de Paris*. Paris: Bachelier, 1847.	HFN 1652; Lesk 36
1853	Otto Funcke (1828-1879) publishes illustrations of crystalline hemoglobin of horse, humans and other species in his *Atlas der physiologischen Chemie*, Leizpig: W. Englemann, 1853.	G-M 684
1858	Charles Darwin and Alfred Russel Wallace publish the first exposition of the theory of natural selection. Darwin and Wallace, "On the Tendency of Species to Form Varieties, and on the Perpetuation of Varieties and Species by Natural Means of Selection," *J. Proc. Linn. Soc.* 3 (1858) *Zool.* 45-62.	G-M 219
1859	Darwin publishes *On the Origin of Species by Means of Natural Selection*, London: John Murray, 1859.	G-M 220
1864	Felix Hoppe-Seyler names the protein crystallized from blood haematoglobulin or haemoglobin. Hoppe-Seyler, "Ueber die chemischen und optischen Eigenschaftern des Blutsfarbstoffs," *Arch. F. path. Anat. U. Physiol.* (Virchow's Archiv) 29 (1864) 233-35.	Judson 490

1865	Working with clearly identifiable traits in the pea plant, (seed color and shape, stem length, position of the flowers) Gregor Mendel discovers a generalized set of rules concerning heredity. He postulates that there are discrete units of heredity (what we call genes) that are transmitted from generation to generation even though some of these are not expressed as an observable trait in every generation. He discovers *dominant* and *recessive* traits— what we call segregation and what we call *alleles*. Mendel, "Versüche über Pflanzen-Hybriden,". *Verh. Naturf. Vereins Brünn* 4 (1866) 3-47. Published in a relatively obscure journal, and dramatically advanced for their time, Mendel's discoveries will ignored by the scientific community until they are rediscovered by de Vries, Correns, and Tschermach in 1900.	Brock ch. 2.1; G-M 222
1870	W. Flemming, Discovery of mitosis	Brock ch. 3.9
1871	Discovery of nucleoprotein, later shown to be the hereditary genetic material: Johann Friedrich Miescher, "Ueber die chemische Zusammensetzung der Eiterzellen," in F. Hoppe-Seyler, *Medicinish-chemische Untersuchungen*, Heft 4 (Berlin, 1871), pp. 441-60.	G-M 695
1871	Wilhelm Preyer (1841-97), best known as a psychologist, describes crystals from nearly 50 species of animals in *Die Blutkrystalle*, Leipzig: Mauke, 1871. Most of these are artificially induced from blood "by adding water to lyse the red blood cells and to solubilize their contents, followed by slight acidification with carbon dioxide.".	Tanford & Reynolds 22
1875	Charles Darwin publishes his ideas for a mechanism of inheritance in the 1875 edition of *The Variation of Plants and Animals under Domestication* [check edition?]. "Darwin advanced a provisional hypothesis that he called pangenesis. He postulated the existence in tissues of minute granules capable of multiplication by self-division; these granules were present in parts of the organism and were collected together to constitute the sexual elements involved in the development of the new generation. He called these granules *gemmules*." (Brock p. 8) Darwin's ideas influence de Vries' hypothesis of *intracellular pangenesis* that ultimately leads to the concept of the gene.	Brock ch. 2.2
1880	Louis Pasteur develops methods for reducing the virulence of a bacterial pathogen. These genetic methods he calls *attenuation* lead to his vaccination for anthrax and rabies. Pasteur, "De l'attenuation du virus du	Brock ch. 3.5

	cholera des poules". *Comptes rendus* 91 (1880) 673-680.	
1881	Robert Koch develops the agar plate technique for isolating pure cultures of bacteria. Using this method in 1882, he isolates the causal agents of tuberulosis, *Mycobacterium tuberculosis*, and cholera, *Vibrio cholerae*.	Brock ch. 3.3
1883	Wilhelm Roux, in *Über die Bedeutung der Kerntheilungsfiguren,* Leipzig: Engelmann, 1883, argues that mitosis insures a precise halving of the nucleus, suggesting that the nucleus contains the material basis of heredity.	G-M 229
1884	Eduard Strasburger publishes *Neue Untersuchungen über den Befruchtungvorgang bei den Phanerogamen als Gründlage für eine Theorie der Zeugung,* Jena: Fischer, 1884, using microscopical evidence to support the hypothesis that the cell nucleus contains the material basis of heredity	G-M 229.1
1886-97	Study of the chemistry of the cell and cell nucleus: Albrecht Kossel, "Zur Chemie des Zellkerns," *Hoppe-Seyl Z. physiol. Chem*. 7 (1882-83): 7-22; 10 (1886): 248-64; 22 (1896-97): 176-87	G-M 702
1888	Theodor Boveri gives decisive proof of the maintenance of chromosomal individuality in "Zellen-Studien," *Jena Z. Naturw*., 1888, **22**-685-882.	G-M 231.1
1889	Hugo de Vries develops his hypothesis of intracellular pangenesis, in which he postulates living, self-replicating units that he calls *pangenes.* "de Vries' pangene subsequently provided the model for the modern gene." (Brock p. 9) de Vries, *Intracellulare Pangenesis*. Jena: Fischer, 1889.	Brock ch. 2.3
1889	Francis Galton presents the first statistical study of biological variation and inheritance in his book, *Natural Inheritance*. (London: Macmillan, 1889)	G-M 233
1889	Richard Altmann, "Ueber Nucleinsäuren," *Arch. Anat. Physiol. Abt.* (1889): 524-36	G-M 713
1893-94	Albrecht Kossel, "Ueber die Nucleinsäure," *Arch. Anat. Physiol., Physiol. Abt.* (1893): 157-64; (1894): 194-203	G-M 719
1894	Emil Fischer provides "provides a structural interpretation of the selectivity of enzymes—their ability to discriminate among very similar molecules, as Pasteur had observed in the fermentation of tartaric acid." (Les p. 36) Fischer writes, "Only with a similar geometrical structure can	

	molecules approach each other closely, and thus initiate a chemical reaction. To use a picture, I should say that the enzyme and substrate must fit each other like a lock and key." (Quoted by Lesk)	
1895	Wilhelm Konrad Röntgen discovers X-rays.	HFN, etc.
1898	Prediction of the polypeptide nature of the protein molecule. In a series of papers through 1912 Kossel proposes "that amino acids and their spatial arrangement with the protein must become the chemical key to understanding of proteins" (Tanford & Reynolds, 52). Albrecht Kossel, "Ueber die Eiweissstoffe," *Dtsch. med. Wschr.* 24 (1898): 581-82. See also paper of 1900 and Herter Lecture in English 1912.	G-M 721; Tanford & Reynolds, Nature's Robots, 52
1900	Rediscovery and confirmation of Mendel's laws almost simultaneously by de Vries, Correns, and Czermach: Hugo de Vries, "Das Spaltungsgesetz der Bastarde," *Ber. dtsch. botanisch. Ges.* 18 (1900): 83-90.	Brock ch. 2.3; G-M 239.01
1900	Rediscovery of Mendel's laws: Carl F. J. E. Correns, "Mendel's Regel über das Verhalten der Nachkommenschaft der Rassenbastarde," *Ber. dtsch. botanisch. Ges.* 18 (1900): 158-67	G-M 239.1
1900	Rediscovery of Mendel's laws: Erich Tschermak von Seysenegg, "Über künstliche Kreuzung von *Pisum sativum, Z. landwirtsch. Versuchsw. in Österreich* 3 (1900): 465-555.; reprinted in *Ber. Dtsch. Botanisch. Ges.* 18 (1900) 232-239	G-M 239.2
1900	Martinus Beijerinck applies de Vries' mutation theory to bacteria.	Brock ch. 4.1
1900	F. Dienert, First adaptive enzyme	Brock ch. 10.1
1901	E. Wildier,s First growth factor in a microorganism	Brock ch. 3.8
1903	Support for Mendelian law of inheritance: Wilhelm Johannsen, *Ueber Erblichkeit in Populationen und in reinen Linien* (Jena: Fischer, 1903).	G-M 242
1903	Chemical distinction between DNA and RNA: Phoebus A. T. Levene, "Darstellung und Analyse einiger Nucleinsäuren," *Hoppe-Seyl. Z. physiol. Chem.* 39 (1903): 4-8, 133-35, 479-83	G-M 725.1
1903	Walter S. Sutton, in his "The Chromosomes in Heredity" (*Biol. Bull.* 4 [1903]: 231-51), advances the theory that Mendel's factors are hereditary particles borne on the chromosomes, and that Mendel's laws for his factors are the direct result of chromosome behavior in meiosis	G-M 242.1

1904	A.F. Blakeslee, Discovery of sexual differentiation in a microorganism	Brock ch. 5.1
1906-23	In a series of papers, Emil Fischer shows that animal and vegetable proteins are composed of a series of amino acids united by elimination of water. Published as *Untersuchungen über Aminosäuren, Polypeptide und Proteine* (Berlin: J. Springer, 1906-23)	G-M 730
1907	R. Massini, Discovery of *Escherichia coli-mutabile*, first *lac-negative* mutant	Brock ch. 4.4
1908	Archibald E. Garrod hypothesizes that each biochemical defect, or "inborn error in metabolism" that causes certain hereditary diseases may be caused by an interruption or block in a metabolic sequence due to the congenital lack of a particular enzyme. At this time Garrod's hypothesis concerning a gene-enzyme link cannot be tested. Garrod,"The Croonian Lectures on Inborn Errors of Metabolism," *Lancet* 4 (1908) 1-7. He publishes a book with the same title the following year.	Brock ch. 2.6; Hook & Norman 875
1909	Wilhelm Johannsen coins the term "gene" as the "underlying structure in the organism, that which was transmitted during hybridzation." (Brock) in *Elemente der Exacten Erblichkeitslehre*. Jena: Fischer, 1909. He coins the term *phenotype* to express what is actually observed and can be measured in contrast to *genotype* that he coins "to express the underlying constitution of the organism from which development of the organism begins. This constitution we designate by the word genotype. The word is entirely independent of any hypothesis…" (quoted by Brock p.11).	Brock ch. 2.5
1909	Edward Tyson Reichert and Amos Peaslee Brown publish *The Crystallography of Hemoglobin* and show by studying the crystalline hemoglobin of more than 500 species that these hemoglobins are not identical. "No comparable effort had ever been expended in investigating species differences at the molecular level" (Tanford & Reynolds 23).	Judson, pp. 492-93, 682
1910	Thomas Hunt Morgan demonstrates sex-linked inheritance in "Sex-Linked Inheritance in Drosophila," *Science*, 1910, **32**, 120-22.	G-M 245.2
1911	Morgan, in "Random Segregation versus Coupling" (*Science* 34 [1911]: 384), proposes that Mendelian factors (genes) are arranged in a linear series on chromosomes and that the degree of linkage between two genes on the same chromosome depends on the distance between them. In 1933 Morgan will win the Nobel Prize (Medicine/Physiology) for his studies of the role of the chromosomes in heredity.	G-M 245.3; Brock ch. 2.7

1912	Von Laue, Friedrich, and Knipping discover the first diffraction pattern of X-rays in a crystal— of copper sulfate. W. Friedrich, P. Knipping and Max von Laue, "Interferenz-Erscheinungen bei Röntgenstrahlen," *Sitzungsb. k. Bayer. Akad. Wiss., math.-phys. Klasse* (8 June 1912): 303-22.	PMM
1912 November- 1913 January	Five months after Laue publishes his discovery, William Lawrence Bragg at the age of 22, discovers that the regular pattern of dots produced on a photographic plate by an X-ray beam passing through a crystal could be regarded as a reflection of electromagnetic radiation from planes in a crystal that were especially densely studded with atoms. From this work the younger Bragg derives the "Bragg relation" ($n\lambda = 2d \sin O$). This relates the wavelength of the X-ray to the angle at which such a reflection could occur. "The Diffraction of Short Electromagnetic Waves by a Crystal," read 11 Nov. 1912 and published in *Proc. Cambridge Phil. Soc.* 17 (14 Feb. 1913): 43-57; W. H. Bragg, "X-rays and Crystals," *Nature* 90 (23 Jan. 1913): 572;	HFN 311
1913 July	The Braggs construct the first X-ray spectrometer using crystals as gratings, using a known wavelength to determine the distances between atomic planes—and thus the structure—of crystalline substances. By the end of 1913 the Braggs reduce the problem of crystal structure analysis to a standard procedure. W. H. and W. L. Bragg, "The Reflection of X-rays by Crystals," *Proc. Roy. Soc. London* 88A (1 July 1913): 428-30 and 889A (22 Sept. 1913): 246-48.	HFN 312
1913	Nishikawa and Ono take X-ray diffraction photographs of silk—the first of a biological molecule. They conclude quantitatively "that the material must contain some ordered structure at the molecular level" (Lesk p. 36)	
1913	Proof that the genes are arranged in a linear sequence along the chromosome: Alfred Henry Sturtevant, "The linear arrangement of six sex-linked factors in *Drosophila,* as shown by their mode of association," *J. expl. Zool.* 14 (1913): 43-59	G-M 245.4
1914 August 1-3	Germany declares war on Russia (August 1) and on France (August 3). World War I begins	
1915	Frederick W. Twort discovers a "glassy transformation"— a microbe that is transmissible, filterable, invisible under the light microscope, and does not multiply in the absence of living bacteria. He wonders whether this	Brock ch. 6.1; G-M

	microbe is a virus or an enzyme or whether the virus itself is some kind of enzyme. Twort, "An Investigation on the Nature of the Ultramicroscopic Viruses," *Lancet* 189 (1915) 1241-43.	
1915	Thomas Hunt Morgan, with Alfred. J. Sturtevant, Hermann. J. Muller and Calvin. B. Bridges, publishes *The Mechanism of Mendelian Heredity*. This epoch-making book presents evidence that genes are arranged linearly on chromosomes and that Mendelian laws are demonstrated by observable events occurring in cells. "By 1915 Morgan and his co-workers were able to present the locations on a genetic map for 30 distinct genes of the four *Drosophila* chromosomes" (Brock pp. 14-15)	G-M 246
1916	L.J. Cole and W.H. Wright promote the "pure line" concept in bacteriology. "Pure line is defined by Johannsen as 'the descendants from one single homozygotic organism, exclusively propagating by self-fertilization;' but for our purposes in the case of bacteria, in which reproduction is asexual, it may be taken as the descendants from any single cell. (The term clone is coming to be largely used by biologists to designate the aggregate line of descendants from a single individual when reproduction is vegetative or asexual. . .)" (Cole & Wright, quoted by Brock p. 49). Cole & Wright, "Application of the Pure-Line Concept to Bacteria," *J. Infect. Dis.* 56 (1916) 209-21.	Brock ch. 4.2
1917	Felix d'Herelle, independently of Twort, discovers a microbe-eating virus that he calls "bacteriophage." The is the origin of the modern usage "phage." Incorrectly d'Herelle believes that bacteriophage play a role in immunity and are a potential therapeutic agent. These misconceptions stimulate research on phage. d'Herelle, " Sur un Microbe Invisible Antagoniste des Bacilles Dysentériques," *Comptes rendus* 165 (1917) 373-75.	Brock ch. 6.1
1918	Germany signs the armistice, ending World War I.	
1919	Thomas Hunt Morgan publishes *The Physical Basis of Heredity*, Philadelphia: Lippincott, 1919. In this he first uses the word gene. Previously he had used the term "Mendelian unit" or "factor." "On the basis of genetic analysis, Morgan could present a number of characteristics of genes. 1. A gene could have more than one effect. For instance, insects that	Brock ch. 2.7

	had the white-eye gene not only had white eyes, but also grew slower and had a lower viability. 2. The effects of the gene could be modified by external conditions, but these modifications were not transmitted to future generations. The gene itself was stable; only the character that the gene controlled varied. 3. Characters that were indistinguishable phenotypically could be the product of different genes. 4. 4At the same time, each character was the product of many genes. For instance, 50 different genes were known to affect eye color, 15 affected body color, and 10 affected length of wing. 5. Heredity was therefore not some property of the 'organism as a whole,' but rather of the genes. 6. Genes of the pair did not jump out of one chromosome into another, but changed when the chromosome thread broke as a piece in front of or else behind them. Thus, crossing-over affected linked genes a groups and was a product of the behavior of the chromosome as an entity. Morgan's studies were based, to a great extent, on the availability of a large number of mutants, but the nature of the mutation process itself remained a mystery. . . ." (Brock p. 15).	
1921	Felix d'Herelle publishes an influential book, *Le Bactériophage. Son Role dans l'Immunité,* Paris: Masson, 1921. This describes the life-history of a bacterial virus. English translation, 1926.	
1921	Speaking in December 1921, Hermann J. Muller states that bacteriophage may be a free-living gene. "…there is a phenomenon…of …striking nature, which must not be neglected by geneticists. This is the d'Herelle phenomenon…if these d'Herelle bodes were really genes, fundamentally like our chromosome genes, the would give us an utterly new angle from which to attack the gene problem…we cannot categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists, physicists, simultaneously with being zoologists and botanists? Let us hope so" (Muller)	Brock ch. 1.1, 2.8; Judson p. 30-31.

	Brock p. 16: "According to Carlson (1981), when Muller completed his lecture that included the mention of phage as a possible gene analog, his colleagues thought they had been treated to a fanciful hoax." "It is commonly said that evolution rests upon two foundations—inheritance and variation; but there is a subtle and important error here. Inheritance by itself leads to no change, and variation leads to no permanent change, unless the variations themselves are heritable. Thus it is not inheritance and variation which bring about evolution, but the inheritance of variation, and this in turn is due to the general principle of gene construction which causes the persistence of autocatalysis despite the alteration in structure of the gene itself. (Muller, "Variation due to change in the individual gene," *American Naturalist* 56 (1922) 32-50. "Muller's hope of 1921 is justly famous among biologists. Unlike many inspired conjectures in the history of science, it had in it nothing woolly. Twenty years later, to explore that conjecture—that is, to discovery and explain the relation 'between the genes and them,' the bacterial viruses—developed into one of the two great routes that converged on that ambition 'to grind genes in a mortar' and so to find in chemistry and physics the foundation of the phenomenon of genetics." (Judson p. 31)	
1921	Alexander Fleming discovers lysozyme, his first major discovery before penicillin. Fleming, "On a Remarkable Bacteriolytic Element Found in Tissues and Secretions. *Proc. Roy. Soc*. B 93 (1922) 306-317.	G-M 1910.1
1923	M. Heidelberger and O.T. Avery, The first non-protein antigen, *pneumococcus polysaccharide*	Brock ch. 9.1
1926	John Desmond Bernal develops the reciprocal lattice in X-ray crystallography	Timeline for British Crystallography
1926	James B. Sumner crystallizes the first enzyme—urease. He will share the Nobel Prize in chemistry with John H. Northrop in 1946.	Nobel Prize website
1927	Hermann J. Muller shows that radiation causes mutations that are passed on from one generation to the next. This is the first suggestion that inherited traits might be altered or controlled, and it creates a sensation "Man's most precious substance, the hereditary material which he could pass on to his offspring, was now potentially in his control. X rays could	Brock ch. 4.11; G-M 251.1; Carlson, E. A. An unacknowledged founding of molecular biology: H. J. Muller's

	'speed up evolution,' if not in practice at least in the headlines. Like the discoveries of Einstein and Rutherford, Muller's tampering with a fundamental aspect of nature provoked the public awe. "(Carlson). Muller, "Artificial transmutation of the gene," *Science* 66 (1927): 84-87. Muller will receive the Nobel Prize in 1946 for his work on the genetic effects of radiation	contribution to gene theory, 1910-36. *J. Hist. Biol.* 4 (1971) 149-70.
1928	Frederick Griffith discovers "transformation" – a process involving the uptake of genetic material by a living organism. Griffith injects mice with a mixture of live, avirulent, rough *Streptococcus pneumoniae* Type I, and heat-killed, virulent, smooth *S. pneumoniae* Type II, and observes that this mixture leads to the death of the mice. Live, virulent, smooth *S. pneumoniae* Type II bacteria are recovered from the dead mice, implying that genetic information from the heat-killed virulent strain has somehow been transferred to the avirulent live strain. Frederick Griffith, "The significance of pneumococcal types," *J. Hyg. (Camb.)* 27 (1928): 113-59	Brock ch. 9.3; G-M 251.2
1928	Pauling publishes "The Coordination Theory of the Structure of Ionic Crystals" in which he proposes 5 rules that scientists can use in solving the structure of molecules. Lawrence Bragg calls the second rule, of "electrostatic valence," "Pauling's Law."	Goertzel & Goertzel p. 57
1929	W. L. Bragg develops Fourier series for crystal structure parameters.	Timeline for British Crystallography
1930	John H. Northrop crystallizes pepsin and finds that it is a protein.	Ency. Brit. Ency. On Ezymes (web)
1930	William Astbury, a student of Lawrence Bragg, is the first to study proteins by X-ray analysis. He applies X-ray analysis to the structure of hair, wool, and related fibers, of which the protein keratin is the principal constituent. He identifies two states: α-keratin and β-keratin.	Tanford & Reynolds 80-81
1930	First coherent general algebraic analysis of Mendelian population behavior: Sir Ronald Aylmer Fisher, *The Genetical Theory of Natural Selection* (1930).	G-M 253
1931	Sir Archibald Edward Garrod publishes *The Inborn Factors in Disease* (1931). He argues that chemical individuality can result in individuals having a predisposition to certain diseases, a view that becomes more widely appreciated after the establishment of recombinant DNA methods to identify inherited genetic defects.	G-M 253.2

1931	Linus Pauling publishes "The Nature of the Chemical Bond. Application of Results Obtained from the Quantum Mechanics and from a Theory of Paramagnetic Susceptibility to the Structure of Molecules" in *J. Am. Chem. Soc.* This is the first exposition of Pauling's "six rules."	Goertzel & Goertzel pp. 70-77
1932	Niels Bohr delivers a lecture on *Light and Life* in which he suggests that life processes are complementary to the laws of chemistry and physics. His speech sparks the interest in biology of Max Delbrück and directs Delbrück's interests away from physics to biology.	
1934	M. Schlesinger, Purification of phage and demonstration of the presence of DNA	Brock ch. 6.12
1934	Arthur Lindo Patterson publishes "A Fourier Series method for the Determination of the Components of Interatomic Distances in Crystals."	Judson 112
1934	John Desmond Bernal and Dorothy Crowfoot (Hodgkin) take the first X-ray photograph of a protein structure—crystalline pepsin. They show that crystals of pepsin give an x-ray diffraction pattern, beginning protein crystallography. This may also be the beginning of "structural biology."(25 years later, in 1958-60, the first complete 3-dimensional structures of proteins, myoglobin and hemoglobin, will be solved by John Kendrew and Max Perutz.)	
1934	Astbury speculates that "fibrous structures might be the basis for the basis for the crystallinity [of pepsin as discovered by Bernal and Crowfoot]: globular proteins in general might be folded from elements essentially like elements of fibrous proteins!" (Tanford & Reynolds 83). "How right he proved to be, but that was much later. Bernal in his biography of Astbury considered this recognition that there might be no radical difference between fibrous and crystalline proteins as one of his great contributions. Overall in Bernal's words Astbury 'influenced everybody's thinking about large biological molecules' and 'was the father of all those who since then interpreted other types of fibrous structure…and who can recognize types of twist from the pattern of blurs on rather obscure fields." (Tanford & Reynolds 83).	Tanford & Reynolds.
1935	Wendell M. Stanley crystallizes tobacco mosaic virus. *Science* 81 (1935) 644-645, 1935).	Brock ch. 6.12
1935	"Target theory": Nikolai Vladimirovich Timofeeff-Ressovsky, K. G. Zimmer and Max Delbrück, "Ueber die Natur der Genmutation und der	G-M 254.1

	Genstruktur," *Nachr. Ges. Wiss. Göttingen, math-fis. Kl.*, Fachgr. 6, 1 (1935): 189-245. This paper represents the debut in genetics of the physicist, Max Delbrück. The three authors "concluded that a mutation is a molecular rearrangement within a particular molecule, and the gene a union of atoms with which a mutation, in the sense of a molecular rearrangement or dissociation of bonds, can occur. The actual calculations of the size of the gene, deduced from calculations on the assumption of a spherical target, were not cogent, as Delbrük wryly admitted in his Nobel Prize lecture, but the entire approach to the problem of mutation and the gene adopted by the three collaborators was highly stimulating to other investigators." (DSB 18, 922.) This work acknowledges the contributions of Hermann Muller in the laws of radiation genetics. Muller spent the year 1933 working in Timofeef-Ressovsky's laboratory in Berlin.	Brock ch. 6.3
1936	E. Wollman and E. Wollman, Lysogeny is due to incorporation of phage into host cell	Brock ch. 7.3
1938	Felix Haurowitz in Prague discovers that crystalline deoxyhemoglobin changes in shape and color on reaction with oxygen, suggesting that it is a molecular lung. Haurowitz, F. "Das Gleichgewicht zwischen Hämoglobin and Sauerstoff," *Hoppe-Seyl. Z. Physiol. Chem*. 254 (1938) 266-72. (In 1949 James D. Watson will take Haurowitz's course on proteins and nucleic acids at Indiana University).	Perutz, Science is Not a Quiet Life, xviii.
1939	Emory L. Ellis and Max Delbrück conduct first experiments on phage, called the "one-step growth experiment," proving that "lysis of the host bacteria and release of the daughter burst of phage indeed occur strictly on the dot [i.e. precise time interval.]" (Judson p. 33).	Brock ch. 6.3
1939	Linus Pauling publishes *The Nature of the Chemical Bond and the Structure of Molecules and Crystals*, his book-length exposition of ideas first developed in 1931	Goertzel & Goertzel p. 77.
1939 September 1	Germany invades Poland. World War II begins	
1941	Beadle and Tatum publish the results of their experiments with the fungus *Neurospora crassa*. They conclude that ultraviolet light treatment somehow causes a mutation in gene that controls the synthesis of an	Brock ch. 5.1 Judson, pp. 189, 661;

	enzyme involved in the synthesis of the essential nutrient. They also show that the defect is inherited in typical Mendelian fashion. This leads to the one-gene / one-enzyme hypothesis, opening up the field of biochemical genetics. G.W. Beadle and E.L. Tatum, "Genetic Control of Biochemical Reactions in *Neurospora*," *Proc. N. A. S.* 27 (1941): 499-506. Beadle and Tatum will share the Nobel Prize with Joshua Lederberg in 1958 for their researches on the mechanism by which the chromosomes in the cell nucleus transmit inherited characters. The "one gene-one enzyme" dogma has since been modified slightly to state that one gene directs the synthesis of one polypeptide—one protein or protein component since it is now known that some proteins are comprised of more than one polypeptide subunit, and that two or more genes may contribute to the synthesis of a particular protein. In addition some products of genes are not enzymes per se but structural proteins.	G-M 254.3
1941	Fritz Albert Lipmann discovers co-enzyme A and its importance for intermediary metabolism, and publishes it in "Metabolic Generation and Utilization of Phosphate Bond Energy" (*Advances in Enzymology* 1 [1941]: 99-162). This discovery illuminates "the process by which cells make available the energy to drive their manufacturing processes" (Judson, p. 245). Lipmann will share the 1953 Nobel Prize in Medicine/Physiology. In his Nobel Lecture (1953) he will speak "very tentatively" of the first clues that "may foreshadow" extension of his concept to proteins and nucleic acids.	Judson, pp. 246-48
1941 December 7	Japan's attack on Pearl Harbor causes the United States to declare war on Japan. Within days Germany and Italy declare war on the United States	
1941	Bernal and Fankuchen show that tomato bushy stunt virus (TBSV) and tobacco mosaic virus (TMV) give clear X-ray diffraction patterns. Bernal and Fankuchen, *J. Gen. Physiol*. 25 (1941) 111-146	History of Structural Virology Timeline
1943	S.E. Luria and M. Delbrück demonstrate via the fluctuation test that mutational alterations occur randomly and before exposure to exogenous mutagenic influences, and that inheritance in bacteria is subject to natural selection. They perform the first quantitative study of mutation in bacteria. Luria, S. E. and Delbrück, M. "Mutations of bacteria from virus sensitivity to virus resistance." *Genetics* 28 (1943) 491-511. Alfred Hershey joins the "phage group" at this time.	Brock ch. 4.8**; Judson p. 37

1944	Erwin Schrödinger publishes *What is Life? The Physical Aspect of the Living Cell* (Cambridge: University Press, 1944), a work speculating about the physical basis of biological phenomena. The work influences the young James D. Watson and others. Actually the book is a popularization of ideas developed by Delbrück in his paper with Timofeeff-Ressovsky in 1935. Brenner points out a fundamental mistake in Schrödinger's understanding of how genes would operate: "Anyway, the key point is that Schrödinger says that the chromosomes contain the information to specify the future organism and the means to execute it. I have come to call this 'Schrödinger's fundamental error.' In describing the structure of the chromosome fibre as a code script he states that. 'The chromosome structures are at the same time instrumental in bringing about the development they foreshadow. They are code law and executive power, or to use another simile, they are the architect's plan and the builder's craft in one.' [Schrödinger, p. 20,]. What Schrödinger is saying here is that the chromosomes not only contain a description of the future organism, but also the means to implement the description, or program, as we might call it. And that is wrong! The chromosomes contain the information to specify the future organism and a description of the means to implement this, but not the means themselves. This logical difference was made crystal clear to me when I read the von Neumann article [Hixon Symposium] because he very clearly distinguishes between the things that read the program and the program itself. In other words, the program has to build the machinery to execute itself." (Brenner, *My Life*, 33-34)	Judson, pp. 29, 32, 42, 77, 87-88, 250-51, 275, 375
1944	The transforming principle is DNA: publication of Oswald T. Avery, C. MacLeod, and M. McCarty, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types. Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III," *J. Exp. Med.* 79 (Feb. 1944): 137-58	Brock ch. 9.5** Judson, pp. 16-18, 19-22, 38-45, 696 G-M 255.3
1945	Edward L. Tatum and George W. Beadle isolate "nutritional (biochemical mutants in the fungus *Neurospora crassa*, making possible the study of rare genetic events because of the power of nutritional selection. The Beadle/Tatum experiments also lead to the one-gene/one-enzyme concept, the first real insight into the connection between	Brock ch. 5.1**

	genotype and phenotype."(Brock p.3) Beadle, G. W. "Biochemical genetics" *Chemical Reviews* 37 (1945) 15-96. "However, the hypothesis did not state in so many words that the gene contained all the information for the enzyme. Indeed, it was considered that the gene was also protein (or nucleoprotein), and one model was that the gene imposed, directly or indirectly, a specific configuration on the enzyme." (Brock p. 77).	
1945 March	Keith R. Porter, Albert Claude, and Ernest F. Fullam publish the first electron micrograph of an intact cell that has been fixed and stained with OsO4. Magnified 1600 times the micrograph reveals mitochondria, the Golgi apparatus and what Porter later names the "endoplasmic reticulum". Porter, Claude and Fullam, "A Study of Tissue Culture Cells by Electron Microscopy." *J. Exp. Med.* (1945).	Rockefeller Univ. Celebrating 50 Years of Electron Microscopy. Www.Rockefeller.edu /rucal/journey/ journey.html
1945 April 25	The collapse of the Third Reich occurs after the meeting of Western and Russian armies at Torgau in Saxony.	
1945 May 7-8	Unconditional surrender of Germany takes place.	
1945 August 14	The surrender of Japan marks the end of World War II	
1945	E.L. Tatum First double mutants in E. coli. "The fact that two or more biochemically distinct requirements were obtained in the same mutant was considered significant in terms of bacterial heredity. Since crossing was not yet possible, these double mutants provided the only evidence for heredity in bacteria. 'This is presumptive evidence for the existence of genes in bacteria' [Tatum]" (Brock p. 79).Tatum, E. L. "X-ray Induced Mutant Strains of *Escherichia coli*." *Proc. Nat. Acad. Sci.* 31 (1945) 215-19.	Brock ch. 5.2
1946	Explicit statement of the one-to-one relation between gene and enzyme: George Beadle, "Genes and the Chemistry of the Organism," *American Scientist* 34 (1946): 31-53, 76	Judson, p. 661
1946	M. Delbrück and W. T. Bailey, "Induced mutations in bacteriophage," Cold Spring Harbor Symp. Quant. Biol. II (1946) 33-50. Mixed phage infection leads to genetic recombination.	Brock ch. 6.9
1946	Discovery of sexual processes in the reproduction of bacteria. First	Brock ch. 5.3; G-M

	crosses in *E. coli* K-12: Joshua Lederberg and E. L. Tatum, "Gene Recombination in *Escheria coli," Nature* (1946) 158: 558. Lederberg, Tatum and Beadle will share the Nobel Prize in 1958.	255.4
1947	Jean Brachet, "Nucleic Acids in the Cell," *Experientia* 3 (15 Jan. 1947): 214-15. Suggestion that ribonucleoprotein granules might be agents of protein synthesis."	Judson, pp. 244-45, 662
1947	Joshua Lederberg produces the first genetic map in *E. coli* K-12. Lederberg, "Gene Recombination and Linked Segregations in *Escherichia coli," Genetics* 32 (1947) 505-25.	Brock ch. 5.3
1948	Sven Furberg, a Norwegian scientist working at Birkbeck College under J. D. Bernal, conducts researches leading to the first correct determination of the structure of a nucleotide, the main building block of DNA. Furberg is the first to propose a helical structure for DNA and the first to attempt building a model of DNA nucleotides. His paper models are pasted into the back of the laboratory notebook	Judson, p. 94.
1948	A.D. Hershey and R. Rotman, First phage genetic map	Brock ch. 6.9
1949	R.D. Hotchkiss, First chemical analysis of bases in transforming DNA	Brock ch. 9.8
1949	Linus Pauling publishes "Sickle-cell Anemia, a Molecular Disease" *Science* 110 (1949) 543-48. This begins the molecular approach to disease.	G-M, Perutz, Science is not a quiet life
1949 May	Maurice Wilkes's EDSAC is fully operational at Cambridge, England. On May 6 it runs a program written by Wilkes for calculating a table of squares. It also runs a program written by David Wheeler for calculating a sequence of prime numbers, becoming the first easily used, fully functional stored-program computer to run a program.	
1949	Dorothy Hodgkin, X-ray analysis of the structure of penicillin	Timeline for British Crystallography
1949	Perutz publishes "An X-Ray Study of Horse Methaemoglobin. II," *Proc. Roy. Soc. London* A 195 (1949): 474-99. It contains Perutz's complete three-dimensional Patterson synthesis of methemoglobin of horse. "During the war I used the nights when I was on duty fire watching in the Cavendish Laboratory to take X-ray pictures throughout the night, getting up from my camp-bed every two hours to change films. Two assistants…shared with me the excruciating tedious and eye-straining job	Judson, p. 525

	of indexing the reflections and measuring their intensities visually again a scale made by exposing the same reflection from a standard anthracene crystal for different times. The London firm that had calculated Dorothy Hodgkin's three-dimensional Fourier of penicillin [Comrie's Scientific Computing Service] did the Fourier summation, using punched card computers of the Hollerith type. When the Patterson finally emerged after years of hard work. . . ." (Perutz, *Science is not a quiet life*, 39)	
1949 September 20	At the Hixon Symposium in Pasadena, California John von Neumann speaks on *The General and Logical Theory of Automata*. Within this speech he compares the functions of genes to self-reproducing automata. "For instance, it is quite clear that the instruction *I* is roughly effecting the functions of a gene. It is also clear that the copying mechanism *B* performs the fundamental act of reproduction, the duplication of the genetic material, which is clearly the fundamental operation in the multiplication of living cells. It is also easy to see how arbitrary alterations of the system *E*, and in particular of *I*, can exhibit certain typical traits which appear in connection with mutation, which is lethality as a rule, but with a possibility of continuing reproduction with a modification of traits." (pp.30-31). Sydney Brenner reads and is influenced by this brief discussion of the gene within the context of information when the Hixon Symposium is published in 1951. Jeffress, Lloyd A. (ed.) *Cerebral Mechanisms in Behavior.* The Hixon Symposium. New York: John Wiley, 1951. "The brilliant part of this paper in the *Hixon Symposium* is his description of it takes to make a self-reproducing machine. Von Neumann shows that you have to have a mechanism not only of copying the *machine*, but of copying the *information* that specifies the machine. So he divided the machine—the *automaton* as he called it—into three components; the functional part of the automaton, a decoding section which actually takes a tape, reads the instructions and builds the automaton; and a device that takes a copy of this tape and inserts it into the new automaton". Brenner, *My Life in Science*, p. 33: "I think that because of the cultural differences between most biologists on the one hand, and physicists and mathematicians on the other, it had absolutely no impact at all. Of course I want' smart enough to really see then that this is what DNA and the genetic code was	

	all about. And it is one of the ironies of this entire field that were you to write a history of ideas in the whole of DNA, simply from the documented information as it exists in the literature—that is, a kind of Hegelian history of ideas—you would certainly say that Watson and crick depended upon von Neumann, because von Neumann essentially tells you how it's done. But of course no one knew anything about the other. It's a great paradox to me that in fact this connection was not seen." (Brenner, *My Life* 35-36).	
1950	Chemical analyses of different DNAs showing definite proportions of different bases ("Chargaff's Rules"): Erwin Chargaff, "Chemical Specificity of Nucleic Acids and the Mechanism of their Enzymatic Degradation," *Experientia (Basel)* 6 (1950): 201-9	Brock ch. 9.8; G-M 255.6; Judson, pp. 74-75
1950	A. Lwoff and A. Gutmann, Discovery of the nature of lysogeny; coinage of the word "prophage". Demonstrates that "phage production by lysogenic bacterial is a cellular event rather than a population event" (Brock p.4). Lwoff, A. & Guttman, A. "Recherches sur *Bacillus megatherium* lysogène," *Ann. Inst. Pasteur* 78 (1950) 711-39.	Brock ch. 7.4**
1951 June (?)	Pauling and his crystallographer, R. B. Corey, announce the α-helix structure for α-keratin. This is the first discovery of a helix structure for a biological molecule. Pauling, Corey, and Branson, "The Structure of Proteins: Two Hydrogen-Bonded Configurations of the Polypeptide Chain", *Proc. Nat. Acad. Sci. USA* 37 (1951) 205-11.	Judson 88-89; Olby 278-87; Perutz, Science, 45-46
1951 July 9-12	At the second English electronic computer conference held at Manchester J. M. Bennett and John Kendrew present the first report on the application of an electronic digital computer to computational biology, using the EDSAC to compute the Fourier syntheses of the x-ray crystallography of myoglobin.	Origins of Cyberspace
1951 September	Franklin and Gosling, working with Ehrenburg-Spear micro-focus X-ray tube at King's College, take photographs of selected regions of single fibers of Signer DNA. Increasingly exact Patterson of A and B forms are achieved. They observe the transition from crystalline A to non-crystalline B when hydration is increased.	Judson 111-12 "Nobody one had ever done a fibre structure this way before"
1951	E.M. Lederberg, Discovery of bacteriophage *lambda*	Brock ch. 7.5
1952	Perutz and Bragg publish a series of papers on hemoglobin structure: "Arrangement of Polypeptide Chains in Horse Methaemoglobin" (with E.	Judson, pp. 528-29, 533-34, 685-66;

	R. Howells), *Acta Crystallographica* 5 (Jan. 1952): 136-41; "The External Form of the Haemoglobin Molecule. I," *ibid.* 5 (March 1952): 277-83; "The External Form of the Haemoglobin Molecule. II," *ibid.* 5 (May 1952): 323-28; "The Structure of Haemoglobin," *Proc. Roy. Soc. London* A 213 (1952): 425-35	Perutz, Science is not a quiet life, 42-45
1952	The so-called "Waring blender experiment," described in Alfred D. Hershey and Martha Chase's paper "Independent Functions of Viral Protein and Nucleic Acid," (*J. Gen Physiol.* 36 [1952]: 39-56) demonstrates that only the DNA of phage enters the cell in significant amounts.	Brock ch. 6.13; G-M 256; Judson, p. 108**
1952	John Bennett and John Kendrew publish the first paper in a scientific journal on the application of an electronic computer to computational biology. An expansion of a briefer summary published in the Manchester University Computer Conference *Proceedings* (1951), it represents a more thorough presentation intended for x-ray crystallographers. It must have been submitted almost immediately after the Manchester Conference since it was received by *Acta Crystallographica* on July 28, 1951. "Programmes have been devised for computing Patterson and Fourier synthesis in two and three dimensions with the EDSAC. An outline of the methods used is given and future possibilities are discussed. At present a two-dimensional summation of about 400 independent terms for about 2000 points takes 1 ½ hr.; a three-dimensional summation of 2000 terms for 18,000 points takes 9 hr. A method is described whereby the EDSAC, without special modification, can be made to print results directly in contour form with considerable economy in time." (p.[109]). "The computation of Fourier syntheses with a digital electronic calculating machine" *Acta Crystallographica* 5 (1952): 109-116.	Origins of Cyberspace 745
1952 February	Crick, Cochran & Vand paper on theory of helical diffraction published. The Structure of Synthetic Polypeptides. I. The Transform of Atoms on a Helix." *Acta Crystallographica 5* (1952) 109-116. **.** "Crick's full mathematical treatment . . . of the x-ray patterns produced by helical molecules generally" (Judson, *Eighth Day of Creation*, p. 129). The paper gives the formulae for the Fourier transforms of a number of helical structures, and provides evidence that the structure of a synthetic polypeptide was based on the alpha helix of Pauling and Corey. "It was, I believe, the first fairly conclusive experimental evidence for the existence of a helical structure at the molecular level. . . . The main value of this work, seen in	

	retrospect, is that it was **a first step on the road to the discovery of the structure of DNA by Jim Watson and Crick"** (Cochran, "This week's citation classic," *Current Contents* [May 18, 1987]: 16).	
1952	N. Zinder and J. Lederberg discover transduction, the transfer of genetic information by viruses, in *Salmonella*	Brock ch. 8.1
1952 May 2-6	Franklin takes more photographs of B-form. No. 51 is finest yet, showing the characteristic X-shaped "Maltese cross" clearer than before	Judson 135-36, Olby 369-76
1953 March	Franklin writes "Molecular Configuration in Sodium Thymonucleate," illustrating it with her photograph 51. This reports her discovery of "the existence of DNA in 2 forms, and conditions for readily and rapidly changing from one to the other. Its phosphates were on the outside." (Maddox 195). "Nothing is more ironical than the words Rosalind wrote, inserted by hand into her typescript in order to adapt it to accompany the Watson-Crick paper. The alteration transformed own fundamental findings into a 'me-too" effort. The inserted words were: 'Thus our general ideas are consistent with the model proposed by Crick and Watson.' So indeed they should have been consistent, considering that the Watson-Crick model was in large part derived from her work. The striking Photo 51 of the B form of DNA appeared as an illustration to her and Gosling's own paper, with no suggestion that Watson had seen it, let alone been inspired by it. She appended also her comment that the photograph 'is strongly characteristic . . .of a helical structure." (Maddox 211-21)	Maddox 195, 211-12
1953 April 25	Discovery of the self-complimentary double helix structure of DNA: James D. Watson and Francis H.C. Crick, "Molecular Structure of Nucleic Acids. A structure for deoxyribose nucleic acid." *Nature* 171 (1953): 737-38. In this paper they state that, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." "We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M.H.F. Wilkins, Dr. R.E. Franklin and their co-workers at King's College, London."	Brock ch. 9.8; G-M 256.3; Watson & Tooze timeline
1953 April 25	M. H. F. Wilkins, A. R. Stokes and H. R. Wilson, "Molecular Structure of Deoxypentose Nucleic Acids," *Nature* 171 (1953): 738-40 Provides supporting data for Watson & Crick structure	Judson, p. 155, 659

1953 April 25	R. E. Franklin and R. G. Gosling, "Molecular Configuration in Sodium Thymonucleate," *Nature*, 171 (1953) 740-41.	
1953 May 30	How the DNA double helix structure embodies within it the capacity for its own self-replication: James D. Watson and Francis H. C. Crick, "Genetical Implications of the Structure of Deoxyribonucleic Acid," *Nature* 171 (1953): 964-67	G-M 256.3 (note)
1953	Further investigation of the structure of DNA. Maurice H. F. Wilkins, W. E. Seeds, A. R. Stokes and H. R. Wilson, "Helical Structure of Crystalline Deoxypentose Nucleic Acid," *Nature* 172 (1953): 759-62.	G-M 256.4
1953 June 5	Watson presents first general overview of his and Crick's discovery at the Eighteenth Cold Spring Harbor Symposium, on viruses. Watson & Crick, "The Structure of DNA". *Cold Spring Harbor Symposia on Quantitative Biology* XVIII (1953) 123-31. In preparation for the meeting Delbrück has circulated copies of the "triple-offprint" as required reading beforehand.	
1953 July 25	Franklin and Gosling publish the completed Patterson synthesis of the A-form in *Nature*. It is entirely consistent with the proposed model—"We suggest that the unit in structure A is, as in Structure B, two co-axial helical chains running in opposite directions." This is the first independent confirmation that the Watson and Crick model is correct.	
1954	Perutz discovers the heavy atom method will solve the phase problem. Green, D. W., Ingram, V. M., and Perutz, "The structure of haemoglobin. IV. Sign determination by the isomorphous replacement method," *Proc. R. Soc.* A225 (1954) 287-307.	Perutz, Science is not a quiet life,
1954	Solution of the hemoglobin structure in two dimensions: W. L. Bragg and Max Perutz, "The Structure of Haemoglobin VI. Fourier Projections on the 101 Plane," *Proc. Roy. Soc. London* A225 (1954): 315-29. "The structure of haemoglobin is a problem of much greater complexity than any other yet attacked by X-ray analysis. Some tentative solutions of the structure have been proposed in the past, but it has been impossible to prove them either right or wrong. What is novel in the present attack on the problem is the certainty of the results." (from the beginning of this paper p. 315)	Judson, pp. 533, 686
1954	François Jacob and Elie Wollman discover zygotic induction.	Brock ch. 7.5

1954	George Gamov comes up with the idea of a genetic code: “Possible Mathematical Relation between Deoxyribonucleic Acid and Proteins,” *Det Kongelige Danske Videnskabernes Selskab: Biologiske Meddelelser* 22, no. 3 (1954): 1-13. In the fall of 1953 Gamov gave Crick an earlier draft of this paper, entitled “Protein Synthesis by DNA Molecules.”	Judson, pp. 265-66
1954	Linus Pauling wins the Nobel Prize (Chemistry) for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances.	
1955	Frederick Sanger sequences the amino acids of insulin, the first of any protein. His work “revealed that a protein has a definite constant, genetically determined sequence—and yet a sequence with no general rule for its assembly. Therefore it had to have a code” (Judson, p. 188). Sanger will receive the Nobel Prize in chemistry in 1958. [reference needed]	Judson, pp. 88-89, 188
1955	Elie Wollman and François Jacob conduct the interrupted mating experiment and discover the concept of fragmentary gene transfer. “This major discovery, which provided the essential clue to the nature of the *Escherichia coli* mating system, led to the important *interrupted mating experiments*, in which a high-speed blender was used to separate mating pairs after different periods of time. By separating mating pairs at various times, certain genes were found in recombinants earlier than others. By comparing the order of entry as observed in the blender experiments to the genetic map, it could be shown that the time of transfer correlated with the position on the map. Wollman and Jacob suggested that one could actually use the *time of transfer* as a means of expressing the genetic map of *Escherichia coli*, a suggestion that proved to be correct. Interrupted mating subsequently became the basis for the whole system of genetic mapping in *Escherichia coli*.” (Brock p.95). Wollman & Jacob, “Sur le mécanisme du transfert de materiel génétique au cours de la recombinaison chez Escheria coli K 12,” *Comptes rendus* 240 (1955) 2449-2451.	Brock ch. 5.7
1955	Dorothy Hodgkin investigates the structure of vitamin B12	Timeline for British Crystallography
1955	Rosalind Franklin proposes the arrangement of protein subunits in TMV based on X-ray diffraction studies. *Nature* 175 (1955), 379-381, 1955).	History of Structural Virology Timeline

1955	Discovery of an enzyme able to catalyze the removal of a terminal phosphate group from ribonucleoside diphosphates: Marianne Grunberg-Manago and Severo Ochoa de Albornoz, "Enzymatic synthesis and breakdown of polynucleotides; polynucleotide phosphorylase," *J. Amer. Chem. Soc.* 77 (1955): 3165-66. Ochoa de Albornoz will share the Nobel Prize with Arthur Kornberg in 1959 for artificial synthesis of nucleic acids by means of enzymes.	G-M 752.3
1956	Discovery of gene inhibitors, activators, modifiers and inducers in maize: Barbara McClintock, "Controlling Elements and the Gene," *C. S. H. Symp. Q. Biol.* 21 (1956): 197-216.	Judson, pp. 445, 679
1956	H. Tijo and A. Levan establish that human cells contain 46 chromosomes in "The chromosomes of man", *Hereditas* 42 (1956) 1-6.	Genome Timeline, yourgenome.org
1956	M. Demerec and P. Hartman, Fine-structure mapping of the genome using transduction	Brock ch. 8.5
1956	Artificial synthesis of nucleic acids by means of enzymes: Arthur Kornberg, "Enzymic synthesis of deoxyribonucleic acid," *Biochim. Biophys. Acta.* 21 (1956): 197-98	G-M 752.4
1957 Sept.	Crick delivers his paper "On Protein Synthesis," published in *Symp. Soc. Exp. Biol.* 12 (1958): 138-63. In it Crick proposes two general principles: 1) The Sequence Hypothesis: "The order of bases in a portion of DNA represents a code for the amino acid sequence of a specific protein. Each 'word' in the code would name a specific amino acid. From the two-dimensional genetic text, written in DNA, are forced the whole diversity of uniquely shaped three-dimensional proteins" (gnn.tigr.org.timeline), and 2) The Central Dogma. "Information is transmitted from DNA and RNA to proteins but information cannot from a protein to DNA. This paper "permanently altered the logic of biology." (Judson)	Judson, pp. 330-333, 669
1957	Robert Langridge, a doctoral student under Wilkins, is the first to apply a stored-program digital computer (IBM 650) to DNA analysis (PhD. thesis)	http://www.cgl.ucsf.edu/home/rl/
1957	Brenner's "dazzlingly simple" proof that the genetic code is not of the overlapping type—"the first concrete achievement of decoding" (Ycas, *The Biological Code*, p. 42). Brenner's proof consisted in demonstrating logically that 64 triplets were insufficient to code the known sequences of amino acids. "Brenner's paper had the consequence that without	Judson, 327-29

	overlapping there were few restrictions, perhaps none, on amino-acid sequences" (Judson 227) "On the impossibility of all overlapping triplet codes in information transfer from nucleic acid to proteins". *Proc. Nat. Acad. Sci.* 43 (1957). 687-694.	
1958	Synthesis of polynucleotides: Peter Thomas Gilham and Khorana, Har Gobind, "Studies on polynucleotides. I. A new and general method for the chemical synthesis of the C_5'-C_3' internucleotide linkage. Synthesis of deoxyribodinucleotides," *J. Amer. Chem. Soc.* 80 (1956): 6212-22. Khorana shared the Nobel Prize in 1968 for techniques he established for the synthesis of polynucleotides	G-M 752.6
1958	Meselson and Stahl use provide evidence that DNA acts as a template when being copied in replication: Matthew S. Meselson and Franklin W. Stahl, "The Replication of DNA in *Escheria coli*," *Proc. Nat. Acad. Sci.* 44 (1958): 671-82	Brock ch. 9.15; G-M 256.6
1958	Proof that DNA replication involves separating the complementary strands of the double helix	Watson & Tooze timeline
1958	Isolation of first enzyme (DNA polymerase I) that makes DNA in a test tube	Watson & Tooze timeline
1958 May	The "PaJaMo" experiment of Arthur Pardee, François Jacob and Jacques Monod "broke the impasse in Crick and Brenner's comprehension of how information in the sequence of bases in DNA came to be expressed as a sequence of the amino acids in protein, and thus led to the theory of the messenger and the solution of the coding problem" (Judson 390) Pardee, Arthur B. (1921-), Jacob, François (1920-), and Monod, Jacques (1910-76). Sur l'expression et le rôle des allèles "inductible" et "constitutif" dans la synthèse de la β-galactosidase chez des zygotes d' "Escherichia coli." Offprint form *C. r. des séances de l'Académie des Sciences* 246 (28 May 1958. This was recorded definitively in "The Genetic Control and Cytoplasmic Expression of 'Inducibility' in the Synthesis of β-galactosidase by *E. coli*," *J. Molecular Biology* 1 (1959): 165-78.	Brock ch. 10.9; Judson, pp. 390-402, 676
1958-60	John Kendrew solves the first three-dimensional molecular structure of a protein (myoglobin). "A Three-Dimensional Model of the Myoglobin Molecule Obtained by X-ray Analysis" (with G. Bodo, H. M. Dintzis, R. G. Parrish, H. Wyckoff,) *Nature* 181 (1958) 662-666, and	

	"Structure of Myoglobin: A Three-Dimensional Fourier synthesis at 2 Å Resolution" (with R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Phillips, V. C. Shore). *Nature* 185 (1960) 422-27. Kendrew began his investigation into the structure of myoglobin in 1949, choosing this particular protein because it was "of low molecular weight, easily prepared in quantity, readily crystallized, and not already being studied by X-ray methods elsewhere" (Kendrew, "Myoglobin and the structure of proteins. Nobel Prize Lecture [1962]," pp. 676-677). Protein molecules, which contain, at minimum, thousands of atoms, have enormously convoluted and irregular formations that are extremely difficult to elucidate. In the 1930s J. D. Bernal, Dorothy Hodgkin and Max Perutz performed the earliest crystallographic studies of proteins at Cambridge's Cavendish Laboratory; however, the intricacies of three-dimensional structure of proteins were too complex for analysis by conventional X-ray crystallography, and the process of calculating the structure factors by slide-rules and electric calculators was far too slow. It was not until the late 1940s, when Kendrew joined the Cavendish Laboratory as a graduate student, that new and more sophisticated tools emerged that could be used to attack the problem. The first of these tools was the technique of isomorphous replacement, developed by Perutz during his own researches on hemoglobin, in which certain atoms in a protein molecule are replaced with heavy atoms. When these modified molecules are subjected to X-ray analysis the heavy atoms provide a frame of reference for comparing diffraction patterns. The second tool was the electronic computer, which Kendrew introduced to computational biology in 1951. The first electronic computer, the ENIAC, which became operational in Philadelphia in 1945, was 10,000 times the speed of a human performing a calculation. In 1951 Cambridge University was one of only three or four places in the world with a high-speed stored-program electronic computer, and Kendrew took full advantage of the speed of Cambridge's EDSAC computer, and its more powerful successors, to execute the complex mathematical calculations required to solve the structure of myoglobin. Kendrew was the first to apply an electronic computer to the solution of a complex problem in biology.	

	Nevertheless, even with the EDSAC computer performing the calculations, the research progressed remarkably slowly. Only by the summer of 1957 did Kendrew and his team succeed in creating a three-dimensional map of myoglobin at a resolution the so-called "low resolution"of 6 angstroms; thus myoglobin became "the first protein to be solved" (Judson, p. 538). "A cursory inspection of the map showed it to consist of a large number of rod-like segments, joined at the ends, and irregularly wandering through the structure; a single dense flattened disk in each molecule; and sundry connected regions of uniform density. These could be identified respectively with polypeptide chains, with the iron atom and its associated porphyrin ring, and with the liquid filling the interstices between neighboring molecules. From the map it was possible to 'dissect out' a single protein molecule . . . The most striking features of the molecule were its irregularity and its total lack of symmetry" (Kendrew, "Myoglobin," p. 681). The 6-angstrom resolution was too low to show the molecule's finer features, but by 1960 Kendrew and his team were able to obtain a map of the molecule at 2-angstrom resolution. "To achieve a resolution of 2 Å it was necessary to determine the phases of nearly 10,000 reflections, and them to compute a Fourier synthesis with the same number of terms . . . the Fourier synthesis itself (excluding preparatory computations of considerable bulk and complexity) required about 12 hours of continuous computation on a very fast machine (EDSAC II)" (Kendrew, "Myoglobin," p. 682).	
1959	Sydney Brenner develops negative staining method for electron microscopy that had been invented in 1955 by Hall. Brenner, S. & Horne, R. W. "A Negative Staining Method for High Resolution Electron Microscopy of Viruses". *Biochim. Biophys, Acta* 34 (1959) 103-110. "This . . . .took electron microscopy out of the hands of the elite and basically gave it to the people. It gave all the people working in virology a tool that they could use, and really wiped out the profession of electron microscopy in a biological laboratory, because anyone could do it. I think this was important because visualizing phages and sub-phage particles under the microscope generated the ability to begin to think about macromolecular assemblies. And of course the molecular biology of the	Brenner, My Life, 56-57.

	cell is really about how bunches of molecules get together and interact." (Brenner, My Life 56-57)	
1959	F. Jacob and J. Monod, Distinction between regulatory and structural genes	Brock ch. 10.10
1959	Discovery of an enzyme (RNA polymerase) that makes RNA chains on the surface of single-stranded DNA.	Watson & Tooze timeline
1960 February	Perutz and team determine the three-dimensional structure of hemoglobin: Perutz, Rossmann, M.; Cullis, A.; Murhead, H.; and Will, G. "Structure of Haemoglobin. A Three-dimensional Fourier Synthesis at 5.5Å Resolution, Obtained by X-ray Analysis" *Nature* 185 (1960) 416-22. The outline of the proteins did not reveal their inner workings. For hemoglobin there was no hint of the mechanism of respiratory transport. "Now, protein structures are solved at the rate of two or three a day, and the power of the method extends to cellular organelles and magadalton molecular structures. Perutz is commonly throught of as a crystallographer, but to him solving the molecular structure was the way to understand the mechanism behind the function. He was, above all, a chemist." Klug, "Max Perutz (1914-2002)", *Science* 295 (2002) 2382-83.	Perutz, Science is not a quiet life, 169, 176
1960	François Jacob, Jacques Monod, *et al* start to elucidate the way in which genes are controlled; they propose that DNA sequences outside the region that codes for protein respond to signals from "operator" genes that encode molecules that "switch" genes on or off. The development of the operon concept. Jacob, F. et al. 'l'Operon: groupe de genes à l'expression coordonné par un operateur. Comptes rendus (1960))245, 1727-29.	Brock ch. 10.10; Genome Timeline. Yourgenome.org
1960	Arthur Kornberg synthesizes DNA in vitro, showing that an enzyme (DNA polymerase) will produce new strands using precursors, an energy source and a template DNA molecule	
1961	Regulatory mechanisms in bacteria: proposal for messenger RNA: François Jacob and Jacques Monod, "Genetic Regulatory Mechanisms in the Synthesis of Proteins," *J. Molec. Biol.* 3 (1961): 318-56. "The grand paper of Jacob and Monod that explained the basic process of regulating gene expression, at least in bacteria" (Brenner, My Life, 119).	Brock ch. 10.10; G-M 256.9
1961	Sydney Brenner, François Jacob, and Matthew Meselson show that short-	Brock ch. 10.12; G-M

	lived RNA molecules, that they call messenger RNA (mRNA) carry the genetic instructions from DNA to structures in the cell called ribosomes. They demonstrate that ribosomes are the site of protein synthesis, "An Unstable Intermediate Carrying Information from Genes to Ribosomes for Protein Synthesis," *Nature* 190 (1961): 576-80	256.10
1961	Crick, Brenner and colleagues propose that DNA code is written in "words" called codons formed of three DNA bases. DNA sequence is built from four different bases, so a total of 64 (4 x 4 x 4) possible codons can be produced. They also propose that a particular set of RNA molecules subsequently called transfer RNAs (tRNAs) act to "decode" the DNA. Francis Crick, L. Barnett, Sydney. Brenner and R. J. Watts-Tobin, "General Nature of the Genetic Code for Proteins," *Nature* 192 (1961): 1227-32. "There was an unfortunate thing at the Cold Spring Harbor Symposium that year. I said, 'We call this messenger RNA' Because Mercury was the messenger of the gods, you know. And Erwin Chargaff very quickly stood up in the audience and said he wished to point out that Mercury may have been the messenger of the gods, but he was also the god of thieves. Which said a lot for Chargaff at the time! But I don't think that we stole anything from anybody—except from nature. I think it's right to steal from nature, however." (Brenner, *My Life*, 85).	G-M 256.8; Judson, pp. 467-68, 680
1961	S. Brenner, F. Crick *et al.*, "The Theory of Mutagenesis," *J. Molecular Biology* 3 (1961): 212-24	Judson, pp. 439, 678; Brenner, My Life, 94.
1961 1961	Use of artificial messenger RNA to deduce the genetic code: J.H. Matthaei and M.W. Nirenberg, "Characteristics and Stabilization of DNAase-Sensitive Protein Synthesis in *E. coli* Extracts," *Proc. Nat. Acad. Sci.* 47 (1961): 1580-88 Nirenberg and Matthaei, "The Dependence of Cell-Free Protein Synthesis in *E. coli* upon Naturally Occurring or Synthetic Template RNA," *Proc. Fifth International Congress of Biochem., Moscow, 10-16 August 1961, Vol. I: Biological Structure and Function on the Molecular Level*, ed. V. A. Engelhardt (N.Y.: Macmillan, 1963), pp. 184-89 (Judson states that in this paper M & N had "solved the coding problem")	Brock ch. 10.12; G-M 256.11; Watson & Tooze timeline; Judson, pp. 453, 679
1962	Watson, Crick and Wilkins are awarded the Nobel Prize for Medicine / Physiology for their discovery of the structure of DNA; Perutz and Kendrew receive the Nobel Prize for Chemistry for their studies of the	Judson, p. 469

	structures of myoglobin and hemoglobins.	
1963	Allen M. Cormack shows that changes in tissue density can be computed from x-ray data. No machine is constructed at this time because of limitations in computing power. This is a key discovery leading in 1972 to the invention of computed tomography (CT).	Origins of Cyberspace
1963	Allosteric interactions. Publication of "first great paper on allosteric proteins": J. Monod, J.-P. Changeux, and F. Jacob, Allosteric proteins and cellular control systems, *J. Molecular Biology* 6 (1963): 306-9	Brock ch. 10.11 Judson pp. 552-53, 687
1964 January	Brenner and colleagues publish the first paper on collinearity, i.e. that there is a simple congruence between the amino acid sequence of a protein and the nucleotide sequence of the gene determining that protein. Sarabhai, Stretton, Brenner & Bolle, Co-linearity of the gene with the polypeptide chain. *Nature* 201 (1964) 13-17.	Brock ch. 10.14
1964	Charles Yanofsky and colleagues, establish that gene sequences and protein sequences are collinear. From this it follows that changes in DNA sequence can produce changes in protein sequence at corresponding positions: Yanofsky, C. et al, On the colinearity of gene structure and protein structure. *Proc. Nat. Acad. Sci. (USA)* 51 (1964) 266-74.	Brock ch. 10.14; Genome timeline. Yourgenome.org
1965	Brenner and colleagues characterize the codons used as stop signals in DNA code. Termination codons (TAA, TAG, TGA) are not recognized by tRNA and act to terminate the growing protein chain. Brenner, S *et al*. "Genetic code: the 'nonsense' triplets for chain termination and their suppression". *Nature* 206 (1965) 994-98.	Genome Timeline, yourgenome.org
1965	David. C. Phillips and associates solve X-ray analysis of Lysozyme at 2Å resolution. This is the second atomic model for any protein, and the first for an enzyme. Blake, C. C. F., Koenig, D. F., Mair, G. A., North, A. C. T., Phillips, D. C. & Sarma, V. R. (1965). *Nature (London)*, **206**, 757. "Certain moments are deeply engraved in my memory. One is the Monday morning in March 1953 when Crick called me into his room to show me his and Jim Watson's double helical model of DNA which immediately revealed the molecular basis of heredity. Another is the moment when David Phillips, Louise Johnson and Charles Vernon made me first understand how an enzyme works." (Perutz) "At the time, transition-state chemistry was so new to me that I did not take in all the	Timeline for British Crystallography; Perutz, Obituary of Phillips: http://www.iucr.org/iucr-top/people/philipd.htm or *J. Synchrotron Rad.* (1999). **6**, 945-946.

	arguments, but the structure and mechanism that were now revealed made me ask why chemical reactions, which normally require powerful organic solvents or strong acids and bases, can be made to proceed in aqueous solution near neutral pH in the presence of enzyme catalysts. Organic solvents have the advantage over water of providing a medium of low dielectric constant, in which strong electrical interactions between the reactants can take place. The non-polar interior of enzymes seemed to me to provide the living cell with the equivalent of the organic solvents used by the chemists. The substrate is drawn into a medium of low dielectric constant in which strong electrical interactions between it and specific polar groups of the enzyme can occur. I felt tempted to add, `Once we understand the stereochemical basis of enzymic catalysis it may become possible to design and synthesize enzymes for specific catalytic functions, for both biological and industrial purposes. I look forward to a future Royal Society Discussion on that subject.' "	
1965	Watson publishes *Molecular Biology of the Gene* (New York: W. A. Benjamin, 1965), the first textbook of molecular biology	
1965	Monod, Lwoff and Jacob receive the Nobel Prize (Physiology / Medicine) for their discoveries concerning genetic control of enzyme and virus synthesis	Judson, p. 565
1967	Szybalski and Summers show that only one strand (the sense strand) acts as a template for transcription of RNA from a DNA template.	Molecular-biologist.com history
1967	Isolation of the enzyme DNA ligase that can join DNA chains together	Watson & Tooze timeline
1968	James Watson publishes *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (New York: Atheneum, 1968)	
1968 August	Perutz opens up "the field of 'molecular pathology,' relating a structural abnormality to a disease." (Klug, "Max Perutz [1914-2002]" *Science* 295 2383.) Perutz, and Lehmann, H. "Molecular Pathology of Human Haemoglobin," *Nature* 219 (1968) 902-09.	Perutz, Science is not a quiet life, 44
1968	De Rosier and Klug describe techniques for the reconstruction of three-dimensional structures from electron micrographs.	Major Events in the Development of the Electron Microscope

		and its Applications to Cell Biology. www.mih.unibas.ch /booklet/lecture/ chapter1/chapter1.html
1968	Robert W. Holley, Har Gobind Khorana and Marshall W. Nirenberg receive the Nobel Prize (Medicine / Physiology) for their interpretation of the genetic code and its function in protein synthesis	Judson, pp. 337, 470
1969	Max Delbrück, Alfred Hershey and Salvador Luria, the three founders of the American phage group, receive the Nobel Prize (Medicine / Physiology) for their discoveries concerning the replication mechanism and the genetic structure of viruses	Judson, p. 587
1970	Hamilton O. Smith and Kent Wilcox isolate the first restriction enzyme-a protein that cuts DNA at specific sites defined by the base sequence. All of molecular biology uses restriction enzymes. Smith & Wilcox. "A restriction enzyme from *haemophilus influenzae*: I. Purification and general properties." *J. Mol. Biol.* 51 (1970) 379-91. Isolation of the first enzyme (the restriction enzyme) that cuts DNA molecules at specific sites	Watson & Tooze timeline; Genome Timeline, yourgenome.org. Brock ch. 11
1970	"The question, however, remained: How does the binding of oxygen to the iron atom of the heme group induce the subunits to change from the deoxy to the oxy structure: As Perutz put it, it is like the flea that makes the elephant jump. Perutz noticed the high-resolution electron density maps of the deoxystructure that the iron atom was displaced by a small but significant amount from the plane of the heme group, whereas in the oxy structure it lay almost in the plane. Armed with a knowledge of metal ion field theory, Perutz realized that this conformational change resulted from a change in the electron spin state of the iron atom, from high spin in the deoxy state to low spin in the oxy state, and hence to a reduction in the radius of the iron. Thus, in the oxy state the iron moves closer into the plane of the heme, and drags with it a protein α-helix to which it is connected. This is the trigger that sets in motion a set of 'molecular levers' that loosen and break the salt bridges, allowing the subunits in the 'tense' deoxy structure to rearrange themselves in the new 'relaxed quaternary oxy structure." (Klug, Max Perutz (1914-2002) 2383. Perutz,	Klug, Max Perutz (1914-2002) 2382-83; Perutz, Science is not a Quiet Life.

	"Stereochemistry of Cooperative Effects in Haemoglobin," *Nature* 238 (1970) 726-39.	
1970	Temin and Baltimore independently report the discovery of reverse transcriptase in RNA viruses. Reverse transcriptase is an enzyme that uses single-stranded RNA as a template for the production of a single-stranded DNA complement to that RNA. This discovery demonstrates the possibility of a flow of genetic information from RNA to DNA. Temin, Baltimore, and Dulbecco will receive awarded the Nobel Prize in Medicine and Physiology in 1975.	Concise history at molecular-biologist.com
1971	The first DNA sequence is produced. Ray Wu and Ellen Taylor deduce the sequence of 12 bases at the ends of the genome of the bacterial virus lambda. Wu and Taylor. Nucleotide sequence analysis of DNA. II. Complete nucleotide sequence of the cohesive ends of bacteriophage lambda DNA. *J. Mol. Biol.* 57 (1971) 491-511.	Brock ch. 11; Genome Timeline; yourgenome.org
1972	Godfrey Hounsfield invents computed tomography (CT), the first application of computers to medical imaging.	Origins of Cyberspace
1972 October	Paul Berg reports the construction of a recombinant DNA molecule comprised of viral and bacterial DNA sequences. David Archer Jackson, Robert Symons, and Paul Berg, "Biochemical Method for Inserting New Genetic Information into DNA of Simina Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of *Escherichia coli*," *Proc. Nat. Acad. Sci.* 69 (1972): 2904-09	G-M 257.3; Watson & Tooze timeline; gnn.tigr.org/timeline
1972	Mertz and Davis confirm that the EcoR1 restriction endonuclease from *Escherichia coli* cuts DNA at a specific site four to six nucleotides long. The DNA sequence that is cut by the restriction enzyme is complementary to other DNAs cut by the same enzyme. This observation paves the way for splicing together of dissimilar sequences and other forms of genetic engineering.	Molecular-biologist.com history
1973	Stanley Cohen, Annie Chang, Robert Helling, and Herbert Boyer demonstrate that if DNA is fragmented with restriction endonucleases and combined with similarly restricted plasmid DNA, the resulting recombinant DNA molecules are biologically active and can replicate in host bacterial cells. Plasmids can thus act as vectors for the propagation of foreign cloned genes. This is the first practical method of cloning a gene and a breakthrough in the development of recombinant DNA	Brock ch. 11; G-M 257.5; Watson & Tooze timeline; Genome Time,

	technologies and genetic engineering. Cohen, Chang, Boyer and Helling, "Construction of Biologically Functional Bacterial Plasmids *in vitro*," *Proc. Nat. Acad. Sci.* 70 (1973): 3240-44	yourgenome.org; gnn.tigr.org/timeline
1973	Daniel Nathans, George Khory and colleagues use recently characterized restriction enzymes to produce the first physical map of a DNA molecule for the virus SV40.	
1973	First public concern that recombinant DNA procedures might generate potentially dangerous, novel microorganisms.	Watson & Tooze timeline
1974	Brenner estimates the number of indispensable genes in the nematode, *C. elegans.* Brenner, S." The Genetics of *Caenorhabditis elegans*," *Genetics* 77 (1974) 71-94. In 1989 John Sulston will map the genome of *C. elegans*. In 1998 its genome will be sequenced—the first of any multi-cellular organism.	Brenner, My Life, 144.
1974	The first of the three Cohen-Boyer recombinant DNA cloning patents is granted, leading to the foundation of the biotechnology industry. .	Hughes, "Making Dollars Out of DNA," *Isis* 92(2001) 541-75.
1975	"The genome of the MS2 virus of bacteria (made of RNA, not DNA) is the first genome to be sequenced."	Genome Timeline yourgenome.org
1975	The overwhelming number of genes in a human cell presents a major hurdle for researchers who wish to detect in a person's DNA a specific disease-fostering gene. Researchers had used the genetic code to determine the DNA sequence that codes for the series of amino acids that make up part of the hemoglobin protein. But they had no means of sifting the telltale DNA out of the DNA of the 100,000 other genes in a human cell, so that they could tell whether the gene was normal or not. Edward Southern develops a powerful method, later called Southern blotting, to pinpoint a specific genetic sequence. He describes a "new analytical tool involving the capillary transfer of restricted DNA fragments from a sizing gel to a nitrocellulose membrane, resulting in an exact replica of the DNA fragments in the gel on the membrane. A specific radio labeled probe is then applied to the membrane under hybridizing conditions. Subsequent exposure of the membrane to photographic film reveals which DNA fragments are homologous to the specific probe used in the	Molecular-biologist.com history

	experiment. This technique allows researchers to determine a physical map of restriction sites within a gene in its normal chromosomal location and provides an estimate of the copy number of a gene in the genome along with information on the degree of similarity of the gene in question to other known homologous sequences. " (m-b.com)	
1975	Paul. Berg *et al*. The Asilomar Conference (at Asilomar, California) on recombinant DNA urges adoption of guidelines regulating recombinant DNA experimentation, and calls for the development of safe bacteria and plasmids that cannot escape from the laboratory	Brock ch. 11 Watson & Tooze timeline
1976	Release of first guidelines by the National Institutes of Health; prohibition of many categories of recombinant DNA experimentation. Rising public concern that the guidelines might not be effective. *New York Times Magazine* article urges prohibiting the awarding of the Nobel Prize for recombinant DNA research	Watson & Tooze timeline
1976	First reported protein crystallography experiments at a synchrotron. At the Stanford synchrotron U.S.A. Phillips, J.C. Wlodawer, A. Yevitz, M.M & Hodgson, "Applications of synchrotron radiation to protein crystallography: primary results," *Proc. Nat. Acad. Sci. USA* **73** (1976) 128-132	http://www.dl.ac.uk /SRS/PX/history /history.html
1976	Transfer RNA: F. H. C. Crick, S. Brenner, A. Klug and G. Pieczenik, "A Speculation on the Origin of Protein Biosynthesis," *Origins of Life* 7 (1976).	Judson, pp. 337-38, 670
1977	Walter Gilbert and Allan M. Maxam devise technique for sequencing DNA. "The Gilbert-Maxam method involved multiplying, dividing, and carefully fragmenting DNA. A stretch of DNA would be multiplied a millionfold in bacteria. Each strand was radioactively labeled at one end. Nested into four groups, chemical reagents were applied to selectively cleave the DNA strand along its bases—adenine (A), guanine (G), cytosine (C) and thymine (T). Carefully dosed, the reagents would break the DNA into a large number of smaller fragments of varying length. In gel electrophoresis, as a function of DNA's negative charge, the strands would separate according to length—revealing, via the terminal points of breakage, the position of each base." (http://gnn.tigr.org/timeline/timeline_frames.shtml)	
1977	Frederick Sanger and colleagues independently develop the methods for	Genome Timeline

	the rapid sequencing of long sections of DNA molecules. Sanger's method, and that developed by Gilbert and Maxam make it possible to read the nucleotide sequence for entire genes that run from 1000 to 30,000 bases long. Sanger, F., Nicklen, S., and Coulson, A.R. DNA sequencing with chain-terminating inhibitors. *Proc. Nat. Acad. Sci. (USA)* 74 (1977) 5463-67.	yourgenome.org Watson and Tooze timeline gnn.tigr.org/timeline
1977	Formation of the first genetic engineering company (Genentech), specifically founded to use recombinant DNA methods to make medically important drugs. Cohen and Boyer are involved with the company.	Watson & Tooze timeline
1977	Creation of the first recombinant DNA molecules containing mammalian DNA.	Watson & Tooze timeline
1977	Groups led by Phil Sharp, Louise Chow, Rich Roberts and Pierre Chambon provide evidence that genes in higher organisms and their viruses are often split up, with disparate regions "spliced" in the messenger RNA. Chow, L.T. et al. An amazing sequence arrangement at the 5'ends of adenovirus 2 messenger RNA. *Cell* 12 (1977) 1-8. Berget, S. M. et al. Spliced sequence at the 5'-terminus of adenovirus 2 late mRNA. *Proc. Nat. Acad. Sci. (USA)* 74 (1977) 3171-5.	
1977	Sanger and colleagues sequence the first whole DNA genome—that of bacteriophage phi-X174 (5375 bases)/ Sanger. F. et al. The nucleotide sequence of bacterophage phi-X174. *J. Mol. Biol*. 125 (1977) 225-46.	Genome Timeline yourgenome.org
1977	Nester, Gordon, and Dell-Chilton demonstrate the transfer of genes on the *A. tumafaciens* plasmid into infected plant cells, paving the way for genetic engineering of plant species.	Molecular-biologist.com history
1978	Nobel Prize (Medicine / Physiology) awarded to Werner Arber, Daniel Nathans and Hamilton O. Smith for the discovery and use of restriction enzymes	Watson & Tooze timeline
1978	Production of the first human hormone somatostatin by using recombinant DNA	Watson & Tooze timeline
1978	Kurt Wüthrich (1938-) and R. R. Ernst develop methods for solving protein structures by Nuclear Magnetic Resonance (NMR) spectroscopy. "Traditionally, structural biology had relied largely on X-ray crystallography, in which biomacromolecules are analyzed after	Lesk p. 37

	crystallization; however, the conventional technique cannot analyze non-crystallizable substances, nor does it permit conformation analysis in solutions, where biomacromolecules exhibit their biological activity. Dr. Wuthrich developed a new technique for atomic-level determination of protein structures in solution, based on distance geometry, a unique idea for building conformations using atom-to-atom distance information based on the Nuclear Overhauser Effect (NOE) resulting from electron-nucleus interaction induced by nuclear magnetic resonance (NMR).” (Kyoto Prize citation: http://www.inamori-f.or.jp/KyotoPrizes/contents_e/laureates/citation/cit14_at.html) Wüthrich, K. & Wagner, G. “Dynamic model of globular Protein Conformations based on NMR studies in solution”, *Nature* 275	
1979	General relaxation of the NIH guidelines allows viral DNAs to be studied by using recombinant DNA procedures	Watson & Tooze timeline
1980	Construction work begins on the first industrial plant designed to make insulin by recombinant DNA procedures	Watson & Tooze timeline
1980	Sanger and colleagues develop the random shotgun method to prepare templates for DNA sequencing. This paper also describes the use of bacterial viruses to grow DNA and application of a color reaction to detect DNA. Sanger et al. J. Mol. Biol. 143,161-78 [lack title of paper]	Genome Timeline yourgenome.org
1980	Nobel Prize (Chemistry) awarded to Paul Berg, Walter Gilbert and Frederick Sanger for (1) cloning of the first recombinant DNA molecules and (2) development of powerful methods of sequencing DNA. This is Sanger’s second Nobel Prize.	Watson & Tooze timeline; Judson, pp. 89, 599
1981	Public offering of stock in the first recombinant DNA company (Genentech). Valuation by Wall Street in excess of 200 million dollars.	Watson & Tooze timeline
1981	First beam at Synchrotron Radiation Source at Daresbury Laboratory used for Protein crystallography	Timeline for British Crystallography
1981	Eli Lilly receives FDA approval to market the first recombinant protein, human insulin, for the treatment of diabetes.	Molecular-biologist.com history
1982	Sanger and colleagues sequence the entire genome of bacteriophage lambda using a random shotgun technique. This is the first whole genome shotgun (WGS) sequence. Sanger, F. Nucleotide sequence of bacteriophage lambda. *J. Mol. Biol.* 162 (1982) 729-73.	Genome Timeline, yourgenome.org

1982	Aaron Klug receives the Nobel Prize in chemistry for the development of crystallographic electron microscopy and application to measurement of biologically important structures.	
1983	Putney and colleagues recognize that random cloning and sequencing could provide rapid access to the messenger RNAs in the cell: they develop the method later called EST (expressed sequence tag). Ptuney, S.D. *et al*. A new troponin T and cDNA clones for 13 different muscle proteins, found by shotgun sequencing. *Nature* 302 (1983) 718-21.	Genome Timeline your genome.org
1985	Three proposals are made to sequence the human genome. Robert Sinsheimer convenes Santa Cruz meeting that develops the idea of complete characterization of the human genome. Renato Dulbecco (Salk Institute) suggests sequencing the genome to help to understand cancer. Charles de Lisi at the Dept of Energy proposes a project to sequence the genome to help understand radiation damage.	Genome Timeline, yourgenome.org
1985	Kary Mullis and colleagues develop the polymerase chain reaction (PCR) in which DNA molecules are copied, doubling number every cycle. After 21 cycles, one molecule will give rise to a million copies. The method is crucial for many techniques in DNA cloning and genomics. Saiki, R.K. et al. Enzymatic amplication of beta-globin genomic sequences and restriction site analyses for diagnosis of sickle cell anemia. *Science* 230 (1985) 1350-4. [Is this the right paper?]	Genome Timeline, yourgenome.org
1985	Rossmann solves the structure of the common cold virus (rhinovirus). Rossmann *et al*. Nature 317:145-153	History of Virology Timeline
1985	Structure of poliovirus solved. J.M. Hogle, M. Chow and D. J. Filman *Science* 229 (1985) 1358-1365	History of Virology Timeline
1986	First prototype DNA sequencing machine demonstrated by Leroy Hood, Lloyd Smith and colleagues	Genome Timeline yourgenome.org
1987	Olson and colleagues develop method to clone large regions of DNA (100,000 to 200,000 base-pairs). Burke et al. Cloning of large segments of exogenous DNA into yeast by means of artificial chromosome vectors. *Science* 236 (1987) 806-12.	Genome Timeline yourgenome.org
1987	Applied Biosystems puts first commercial DNA sequencing machine, based on Hood's technology, on the market	Genome Timeline yourgenome.org
1987	Formal proposals by Department of Energy in US to sequence the human	Genome Timeline,

	genome. Report at Oak Ridge National Laboratory Genome website. Cost predictions for the human genome sequence. It is estimated that one worker can produce about 50,0000 bases of finished DNA sequence per year at a cost of about $1-$2 per base. Thus the human genome would take 60,000 person-years and cost $3-6 billion to complete.	yourgenome.org
1988	Hermann Waldmann & Greg Winter produce humanized rat anti-T-cell antibody that induces prolonged remissions in two terminally ill leukemia patients. This may be the first bio-engineered antibody. Reichmann, L.; Clark, M.; Waldmann, H, Winter, G. Reshaping human antibodies for therapy. *Nature* 332, 323-27.	Perutz, *Protein Structure* (1992) xi
1989	John E. Sultson, Robert H. Waterston, Coulson and colleagues present genome map of *C. elegans* at Cold Spring Harbor meeting. This result stimulates efforts to sequence the genome as a model for the human genome project.	Genome Timeline, yourgenome.org
1989	"Cystic Fibrosis gene" identified. Teams under Francis Collins and Lap-Chee Tsui identify the gene for the cystic fibrosis transmembrane receptor (CFTR) that, when mutated, can lead to onset of cystic fibrosis. [NLM pp. CFTR.]	Genome Timeline, yourgenome.org
1990	US Department. of Energy and National Institutes of Health submit a formal proposal to Congress for a 15-year project to sequence the human genome	Genome Timeline, yourgenome.org
1990	The first approved gene therapy is performed with some success. Immunoglobulin genes are inserted into harvested white blood cells that are then returned to the patient and confer some immunity.	Molecular-biologist.com history
1990	David Lipman, Eugene Myers, and colleagues at the National Center for Biotechnology Information (NCBI) publish the BLAST algorithm for aligning sequences.	http://ihome.cuhk.edu.hk/~z045513/
1990	Project to sequence 3 MB of *C. elegans* genome coordinated between UK Medical Research Council Laboratory of Molecular Biology and Washington University, St. Louis. This is jointly funded by the MRC and NIH.	Genome Timeline, yourgenome.org
1990	Sydney Brenner proposes sequencing human cDNAs to provide rapid	Genome Timeline,

	access to human genes." One obvious way of finding at least a large part of the important [fraction] of the human genome is to look at the sequences of the messenger RNAs of expressed genes." Brenner, S. The human genome: the nature of the enterprise. IN: *Human Genetic Information: Science, Law and Ethics.* Ciba Foundation Symposium 149 (1990) 6-12.	yourgenome.org
1990 July	Sequence of human cytomegalovirus (HCMV) genome is completed. This is 0.23MB (229,354bp)	
1991	J. Craig Venter (1946-) describes a fast new approach to gene discovery using Expressed Sequence Tags (ESTs). "Although controversial when first introduced, ESTs were soon widely employed both in public and private sector research. They proved economical and versatile, used not only for rapid identification of new genes, but also for analyzing gene expression, gene families, and possible disease-causing mutations. "ESTs could also facilitate an overview of the whole genetic repertoire of an organism, and in this way helped establish the important discipline of comparative genomics. EST databases were established for various animals, plants, and even fungi. In 1995, in a landmark supplement to *Nature*, the Venter team described some 170,00 ESTs that could be used to identify over 87,000 cDNA sequences from various tissues in the human body—over 80 percent of which were previously unknown." (gnn.tigr.org/timeline) Adams, M.D., Kelley, J.M., Gocayne, J.D., Dubnick, M., Polymeropoulos, M.H., Xiao, H., Merril, C.R., Wu, A., Olde, B., Moreno, R., Kerlavage, A.R., McCombie, W.R., and Venter, J.C. Complementary DNA sequencing: "expressed sequence tags" and the human genome project. *Science* **252**, 1651-1656 (1991).	
1992	Ventor leaves the National Institutes of Health and founds The Institute for Genome Research (TIGR).	Gnn.tigr.org/ timeline/1995
1992	John E. Sulston and Robert Waterston seek funding from the Wellcome Trust for 5-year proposal to sequence 40Mb of the human genome. The Wellcome Trust and the MRC join forces. The Wellcome Trust releases funds to support creating the Sanger Center near Cambridge.	Genome Timeline, yourgenome.org
1992	The entire 315,000-base nucleotide sequence of one of the sixteen chromosomes of the yeast *S. cerevisiae* is published.	Molecular-biologist.com history

1994	In meetings in the U. S. John Sulston and Robert Waterston propose to produce a “draft sequence of the human genome by 2000. This involves emphasizing sequence acquisition and the value of “draft quality sequence” to biomedical research. Marshall, E. A strategy for sequencing the genome 5 years early. *Science* 267 (1994) 783-4.	Yourgenome.org timeline
1995	J. Craig Venter, Hamilton O. Smith, Fraser and colleagues at The Institute for Genomic Research (TIGR) report the first complete genome sequence of a free-living, nonviral microorganism, *Haemophilus influenzae* (H.flu). This genome consists of 1,830,137 base pairs. Fleischmann, R.D. *et al*. Whole-genome random sequencing and assembly of Haemophilus influenzae Rd. *Science*, 269 (1995) 496-512.	Yourgenome.org. timeline; Gnn.tigr.org/ timeline/1995
1995	The entire human genome is mapped, using yeast artificial chromosomes (YACs). Some chromosomes, notably 22, were mapped in fine detail. “The maps were an important step toward clone-based sequencing. Various authors. *Nature* 377 (1995) 175-379. The issue is devoted to the human genome maps.	Yourgenome.org. timeline
1996	An international consortium completes the genome sequence of the yeast *Saccharomyces cerevisiae*	Yourgenome.org
1997 February	The amount of human finished sequence reaches 40MB	Yourgenome.org
1997	The Roslin Institute in Edinburgh reports the birth of Dolly the lamb, the first mammal to be cloned from an adult using the modern techniques of trangenic cloning. The successful cloning of Dolly suggests the possibility that similar techniques could be utilized to clone humans.	Molecular-biologist.com
1998 February	The amount of human finished sequence reaches 110MB.	Yourgenome.org timeline
1998	Founding of public-private SNP Consortium to map Single Nucleotide Polymorphisms. These are “changes in single letters in our DNA code that can act as markers in the DNA landscape. Some SNPs are associated closely with susceptibility to genetic disease, our response to drugs or our ability to remove toxins.”	Yourgenome.org timeline
1998 June	The complete genome sequence of the tuberculosis bacterium, *Mycobacterium tuberculosis*, is published by teams from England, France, U.S. and Denmark. Cole, S.T. et al., “Deciphering the biology of	Yourgenome.org timeline

	Mycobacterium tuberculosis from the complete genome sequence," *Nature* 393 (1998) 537-44.	
1998 September	ABI Prism 3700 sequencing machine becomes available. This capillary-based machine is designed to run about 8 sets of 96 sequence reactions per day	Yourgenome.org timeline
1998	Completion of the first genome of a multi-cellular organism—*C. elegans*. This organism is widely used in a range of biology. The *C. elegans* Sequencing Consortium. Genome sequence of the nematode *C. elegans*: A platform for investigating biology. *Science* 282 (1998) 2012-18.	Yourgenome.org timeline
1999	Researchers in the Human Genome Project led by the Sanger Centre complete sequencing human chromosome 22. This is about 34 million base-pairs and includes at least 550 genes. Dunham, I. *et al*. The DNA sequence of human chromosome 22. *Nature* 402 (1999) 489-95.	Yourgenonme.org timeline
1999 November	The data in the human draft sequence reaches 1000MB	Yourgenome.org timeline
2000	Human Genome Project leaders at the Sanger Centre and the National Human Genome Research Institute announce the completion of a "working draft" DNA sequence of the entire human genome. At the same time Celera Genomics, founded by J. Craig Venter, announces completion of their "first assembly" of the genome. Sanger Centre working draft site. NHGRI news pages.	Yourgenome.org timeline
2000	Teams from the Sanger Centre, colleagues in the UK and Germany, and a group from the Institute for Genome Research (Craig Venter) publish sequences of different strains of *Neisseria meningitides*, the bacterium that causes many cases of meningitis. "The two strains have different properties and comparison of the two sequences was used to look for new vaccine targets." Parkhill, J. *et al*. Complete DNA sequence of a serogroup A strain of Neisseria meningitides Z2491. *Nature* 404 (2000) 502-6.	Yourgenome.org timeline
2000	In collaboration with the Pasteur Institute in Paris, teams from the Sanger Centre sequence the genome of *Mycobacterium leprae*, the causative agent of leprosy."*M. leprae* is extremely difficult to grow in the laboratory and genomic data is expected to speed study of this pathogen". Sanger Centre. *M. leprae* site.	Yourgenome.org. timeline

2000 March	J. Craig Venter's Celera Genomics, in collaboration with the worldwide *Drosophila* community, and the federally funded Berkeley Drosophila Genome Project, sequence and assemble nearly 120MB of the *Drosophila* genome and release it to researchers at publication. "The genome sequence was determined by a whole genome shotgun sequencing strategy supported by clone-based sequencing and a BAC physical map." **Fruitfly**-the Berkeley *Drosophila* Genome Project. **Flybase**-one mirror of a worldwide set of *Drosophila* databases. Eugene W. Myers, Granger G. Sutton, Art L. Delcher, Ian M. Dew, Dan P. Fasulo, Michael J. Flanigan, Saul A. Kravitz, Clark M. Mobarry, Knut H. J. Reinert, Karin A. Remington, Eric L. Anson, Randall A. Bolanos, Hui-Hsien Chou, Catherine M. Jordan, Aaron L. Halpern, Stefano Lonardi, Ellen M. Beasley, Rhonda C. Brandon, Lin Chen, Patrick J. Dunn, Zhongwu Lai, Yong Liang, Deborah R. Nusskern, Ming Zhan, Qing Zhang, Xiangqun Zheng, Gerald M. Rubin, Mark D. Adams, and J. Craig Venter A Whole-Genome Assembly of *Drosophila*. *Science* **287**, 2196-2204 (March 24, 2000).	Yourgenome.org timeline; gnn.tigr.org timeline/ 1999_Drosophila
2001 February	"In a remarkable special issue, *Nature* includes a 60-page article by the Human Genome Project partners, studies of mapping and variation, as well as analysis of the sequence by experts in different areas of biology. *Science* publishes the article by Celera on the assembly of HGP and Celera data as well as analyses of the use of the sequence." *Nature*, The Human Genome. Science, The Sequence of the Human Genome [Get specific references] "Celera Genomics announced the first complete assembly of the human genome. Using whole genome shotgun sequencing, Celera began sequencing in September 1999 and finished in December. Assembly of the 3.12 billion base pairs of DNA, over the next six months, required some 500 million trillion sequence comparisons, and represented the most extensive computation ever undertaken in biology. "The Human Genome Project reported it had finished a "working draft" of the genome, stating that the project had fully sequenced 85 percent of the genome. Five major institutions in the United States and Great Britain performed the bulk of sequencing, together with contributions from institutes in China, France, and Germany." (gnn.tigr.or/timeline/2000)	Yourgenome.org timeline