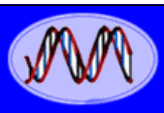
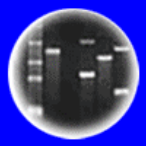

DNA
Genetic Code of Life


Entire Genetic Code of a Bacteria


DNA Fingerprinting


Cloning: Ethical Issues and Future Consequences


Plants of Tomorrow

HC70A, PLSS530, & SAS70A
Winter 2014
Genetic Engineering in Medicine, Agriculture, and Law

Professors Bob Goldberg,
Channapatna Prakash, & John Harada

Lecture 3
What Are Genes & How Do They Work: Part One

UCLA TUSKEGEE UNIVERSITY UCDAVIS UNIVERSITY OF CALIFORNIA

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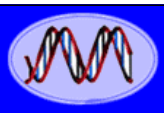
PREVIOUS TWO LECTURES

- Genetic Engineering Origins
- What Can Be Done With Genetic Engineering?
- Classical vs. Molecular Genetic Engineering
- Demonstrations
  - Spooling DNA
  - Vegetables – Classic Genetic Engineering



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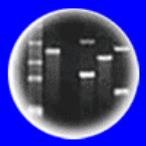

DNA Fingerprinting

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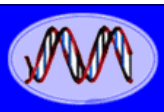
THEMES FOR TODAY'S LECTURE
Gene Structure & Function
Part One (Text Chapter 2)

- What is the Function of a Gene?
- What are the Properties of Genes?
- What is the Evidence That DNA is the Genetic Material (Griffith and Avery Experiments)?
- Is Transformation Universal?
- What is the Structure of DNA?
- What is the Structure of a Chromosome?
- What is the Colinearity Between Genes & Proteins (how does DNA→protein)?
- How Do We Know That Genes Function Independently of One Another?
- What is the Anatomy of a Gene?
- How Do Switches Work to Control Gene Activity?
- What Are the Possibilities For Manipulating Genes in the Future?
- Demonstration: "Bacterial Cloning"



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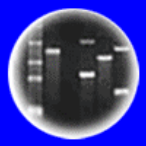

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Recall….Science is NOT "Hocus Pocus" or Based on Opinions and Beliefs

•Science is Based on Observation, Hypothesis Testing, Rigorous Experimentation, and Verification

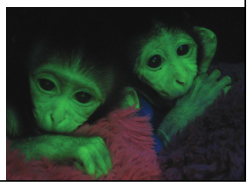
•Technology, or the Application of Scientific Knowledge, Has Transformed Dramatically Our Lives and How We Live

What Are the Data!!!!!

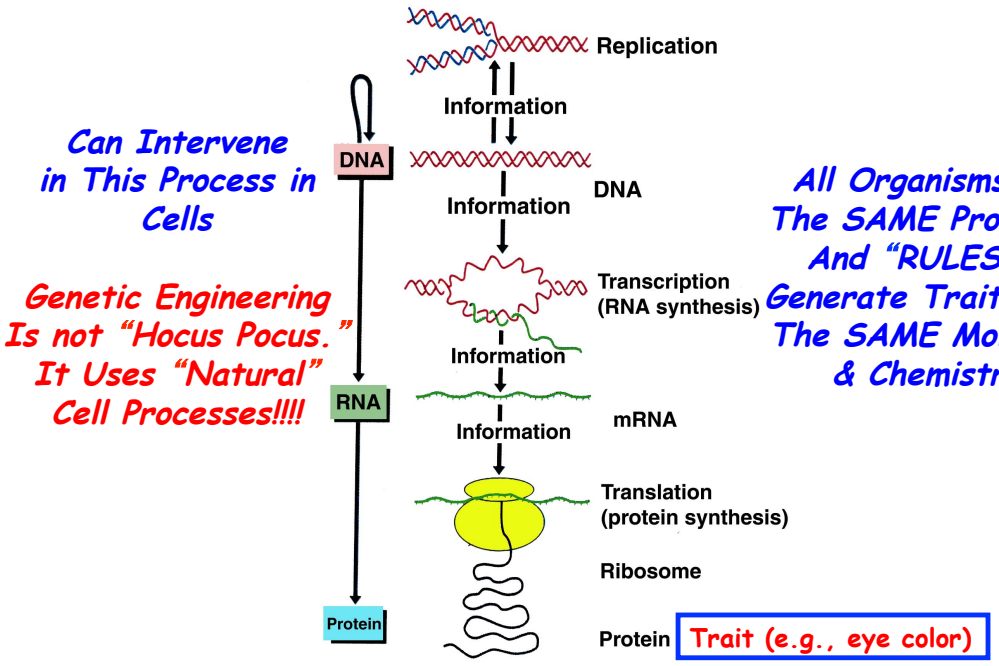
And……Genetic Engineering Is Manipulating DNA *Either Classically or By Exciting Modern Approaches* (GE 1.0 and 2.0)! It's a Scientific Process Not Hocus Pocus

Understanding Genetic Engineering

Requires a Basic Understanding of Genes And How They Work



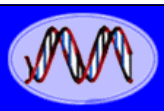
Understanding the Properties of Genes & How Genes Can Specify Traits Is the "Key" to Understanding Genetic Engineering!



Can Intervene in This Process in Cells

Genetic Engineering Is not "Hocus Pocus." It Uses "Natural" Cell Processes!!!!

All Organisms Use The SAME Processes And "RULES" to Generate Traits!! And The SAME Molecules & Chemistry!!



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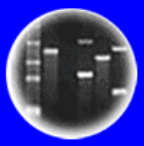

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WHAT ARE THE PROPERTIES OF A GENE?

1. Replication
2. Stability (Mutations)
3. Universality
   a) All Cells
   b) All Organisms
4. Direct Cell Function/Phenotype

Design an Experiment to Show That DNA is The Genetic Material?

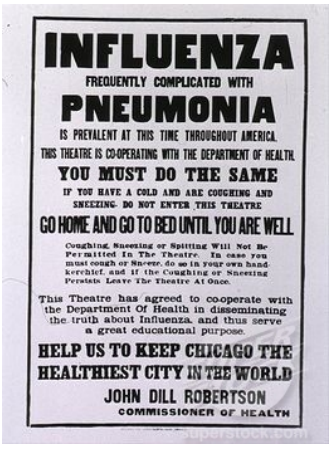
- How Can These Properties Be Tested Experimentally?
- What Predictions Follow From These Properties?

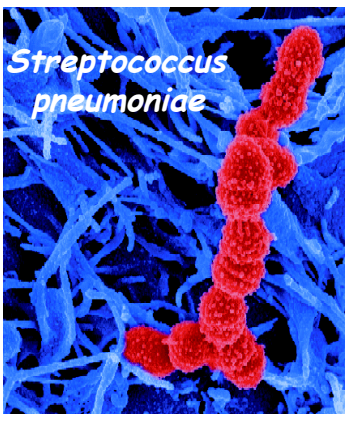
If DNA is the Genetic Material, THEN What……?

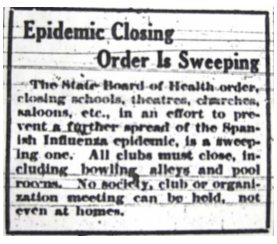
Evidence That DNA Is the Genetic Material Starts With Pneumonia

PNEUMONIA KILLS 990 IN CITY SINCE JAN. 1; Forty-Eight Die in Twenty-Four Hours, Four Fewer Than on Previous Day. 387 INFLUENZA CASES Six More Deaths Reported, but Copeland Sees Chief Danger in First-Named Disease. January 29, 1922 - New York City

Spanish Flu (viral) Was also "Killer" at This Time!







Spanish Flu Killed 50-100 million people world-wide from 1918 to 1920 – Most From Secondary Bacterial Infections

The Spanish Flu Pandemic - 1918 to 1920

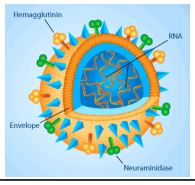
It is estimated that anywhere from 50 to 100 million people were killed world wide - the approximate equivalent of one third of the population of Europe, more than double the number killed in World War I. This extraordinary toll resulted from a high death rate of up to 50%.

Characterization of the 1918 "Spanish" influenza virus neuraminidase gene PNAS June 6, 2000

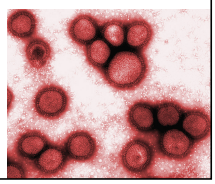
Ann H. Reid,* Thomas G. Fanning, Thomas A. Janczewski, and Jeffery K. Taubenberger

Researchers detect deadly Spanish flu genes

A team of researchers in Japan and the United States have determined the causative genes for the Spanish flu that reportedly claimed the lives of some 40 million people around the world in 1918. PNAS January, 2009



By Sequencing the Virus Genome From Victims Dead For 80 Years & Synthesizing the "Original" Flu Virus By Genetic Engineering



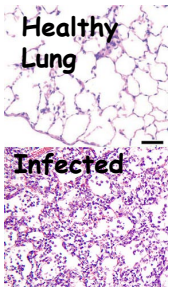
Major Causes of Death in USA

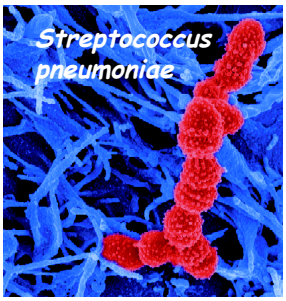
1920 (CDC)	2011 (CDC)
1. Pneumonia	1. Heart Disease
2. Heart Disease	2. Cancer
3. Tuberculosis	3. Chronic Respiratory Diseases (e.g.,Emphysema & Bronchitis)
4. Stroke	4. Stroke
5. Kidney Disease	5. Unintentional Accidents (e.g.,Cars)
6. Cancer	6. Alzheimer's Disease
7. Unintentional Accidents (excluding cars)	7. Diabetes
8. Diarrhea, Enteritis, Intestinal Lesions	8. Kidney Disease
9. Premature Birth	9. Influenza & Pneumonia
10. Maternal Death Giving Birth	10. Intentional Self Harm (Suicide)
	11. Septicemia (Bacteria)
Note: Based on 1.1 M Deaths (1,300 per 100,000). Child Mortality = 100 per 1,000	Note: Based on 2.5M Deaths (741 per 100,000). Child Mortality 6 per 1,000

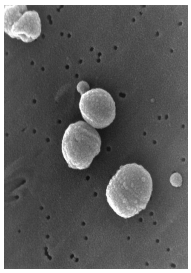
Frederick Griffith & The Transforming Principle

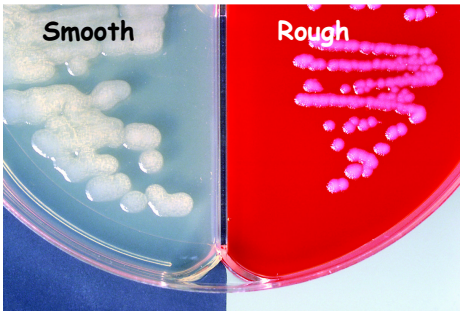
The First Genetic Engineering Experiment *(unintentional!)*

1879-1941



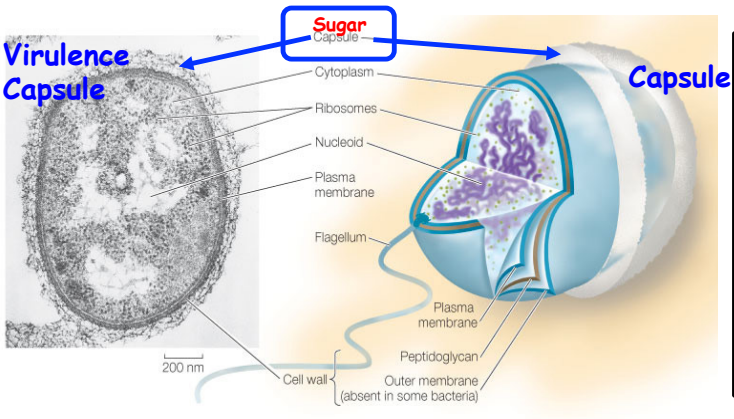




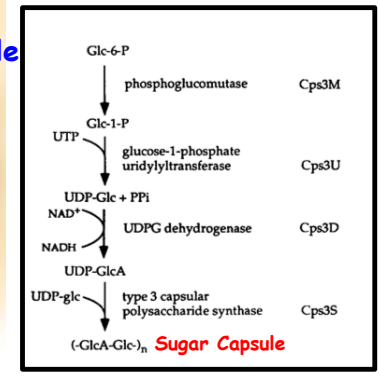


Invented the Word "Transformation"
Not Understood For Another 50 Years

Streptococcus pneumoniae



Capsule Biosynthesis



J. Exp. Med. 181, 973, 1995

The Sugar Capsule Protects the Bacteria From Mammalian Host Antibodies

Capsule = Virulence No Capsule = Avirulence

Bacterial Genome Projects Have Provided Remarkable Insight Into Bacterial Genomes and Cell Functions

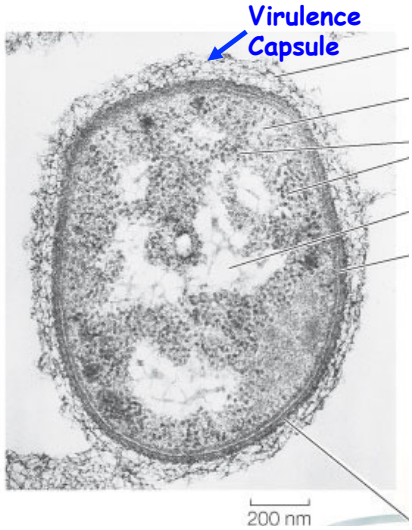
Table 1–1 Some Genomes That Have Been Completely Sequenced

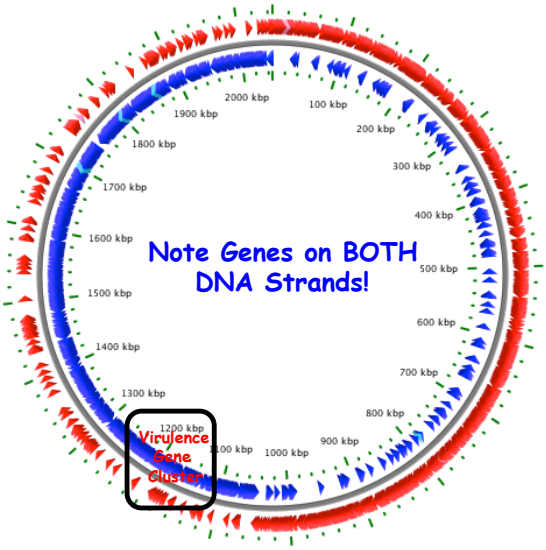
SPECIES	SPECIAL FEATURES	HABITAT	GENOME SIZE (1000s OF NUCLEOTIDE PAIRS PER HAPLOID GENOME)	ESTIMATED NUMBER OF GENES CODING FOR PROTEINS
BACTERIA				400 to 8,000 Genes
Mycoplasma genitalium	has one of the smallest of all known cell genomes	human genital tract	580 Made Synthetically!	468
Synechocystis sp.	photosynthetic, oxygen-generating (cyanobacterium)	lakes and streams	3573	3168
Escherichia coli	laboratory favorite	human gut	4639	4289
Helicobacter pylori	causes stomach ulcers and predisposes to stomach cancer	human stomach	1667	1590
Bacillus anthracis	causes anthrax	soil	5227	5634
Aquifex aeolicus	lithotrophic; lives at high temperatures	hydrothermal vents	1551	1544
Streptomyces coelicolor	source of antibiotics; giant genome	soil	8667	7825
Treponema pallidum	spirochete; causes syphilis	human tissues	1138	1041
Rickettsia prowazekii	bacterium most closely related to mitochondria; causes typhus	lice and humans (intracellular parasite)	1111	834
Thermotoga maritima	organotrophic; lives at very high temperatures	hydrothermal vents	1860	1877

12,982 Bacterial Genomes Have Been Sequenced to Date (January, 2014)

Table 1-1 (part 1 of 2) *Molecular Biology of the Cell*, Fifth Edition (© Garland Science 2008)

Streptococcus pneumoniae Genome Has Been Sequenced!





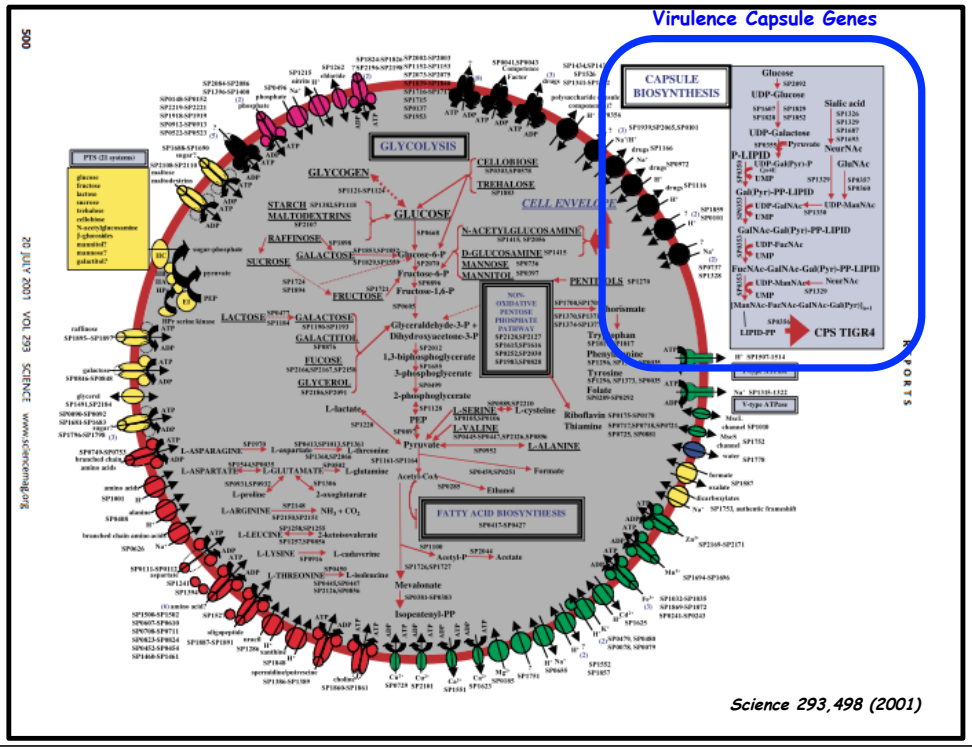
2,160,837 bp and 2,236 Genes

At Least 13 Genes Specify Capsule Formation

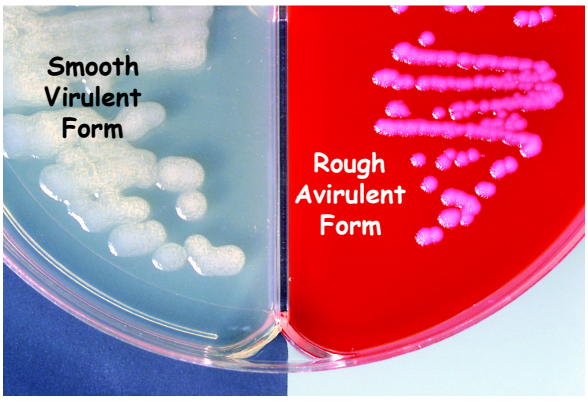
What Happens If One of These Genes Is Mutated?

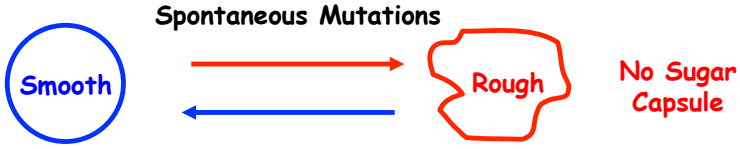
Science 293,498 (2001)

Correlation of *Streptococcus* Genes With Biological Functions (i.e.,Genome Annotation)



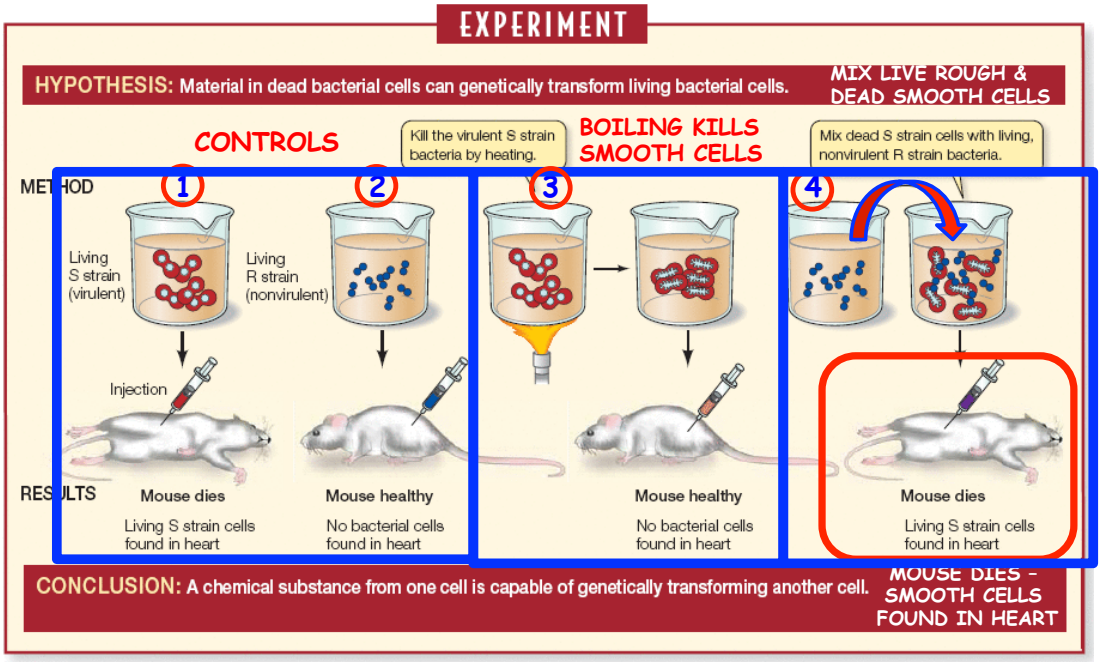
The Griffith Experiment With Smooth and Rough Pneumonia Bacteria





J. Hygiene, 1928

The Griffith Experiment (1928)



LIVE Rough Cells TRANSFORMED by DEAD Smooth Cells!!!
HOW? What Was the Transforming Principle? Hypothesis?

Griffith, 1928, J. of Hygiene, 28 (2), 113-157

VOLUME XXVII JANUARY, 1928 No. 2

THE SIGNIFICANCE OF PNEUMOCOCCAL TYPES.

BY FRED. GRIFFITH, M.B.
(*A Medical Officer of the Ministry of Health.*)
(*From the Ministry's Pathological Laboratory.*)

Inoculation experiments with heated virulent Type I culture and attenuated R strains of Types I and II.

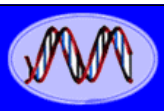
Conversion of R Type II into S Type I. In the experiment in Table VII two out of eight mice injected with heated virulent Type I culture together with an attenuated R culture derived from Type II died of pneumococcal septicaemia and yielded pure S colonies of Type I from the blood; plates from the lesions at the seat of inoculation showed a mixture of R and S colonies.

Table VII.

Killed S pneumococci	Living R pneumococci	No. of mouse	Result	Type of culture obtained from mouse
Type I heated 2 hours at 60° C. Dose = deposit of 50 c.c. of broth culture	None	641	Killed 5 days	None
	,,	642	,, 6 ,,	,,
	,,	643	,, 6 ,,	,,
	,,	644	,, 6 ,,	,,
As above	R 4, Type II. Dose = 0·25 c.c. of blood broth culture	645	Died 3 days	S colonies, Type I
		646	Killed 5 ,,	R cols. from local lesion
		647	,, 6 ,,	,, ,,
		648	,, 6 ,,	,, ,,
As above	R 4, Type II, grown in the heated Type I deposit. Dose = 0·36 c.c.	649	Killed 5 days	R cols. from local lesion
		650	Died 4 ,,	S colonies, Type I
		651	Killed 6 ,,	None
		652	,, 6 ,,	One R colony

Note: R Strain II Transformed into Smooth Strain I

Significance?



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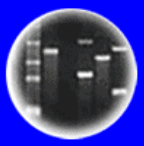

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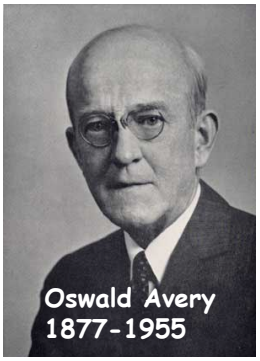
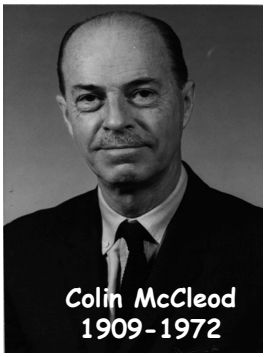
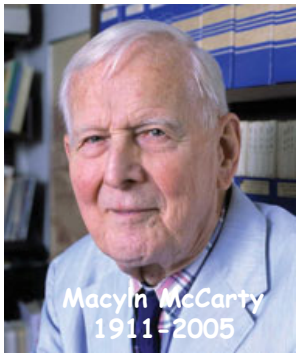
Change of Rough II Strain to Smooth I Strain Indicates that the Change is Due to Mutation or "Something" Else

a. Mutation
b. "Something" Else

What Was The Transforming Principle? Experiments of Avery, McCleod, & McCarty Fast Forward to the 1940s!



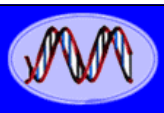




DNA is the Genetic Material!

One of the Major Reasons Watson and Crick Considered DNA As the Genetic Material In Order to Solve DNA Structure

J. Exp. Med.,1944



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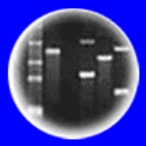

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STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES

OSWALD T. AVERY, COLIN M. MACLEOD, AND MACLYN MCCARTY

J. Of Experimental Medicine, 79 (2), 137-158 (1944)

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

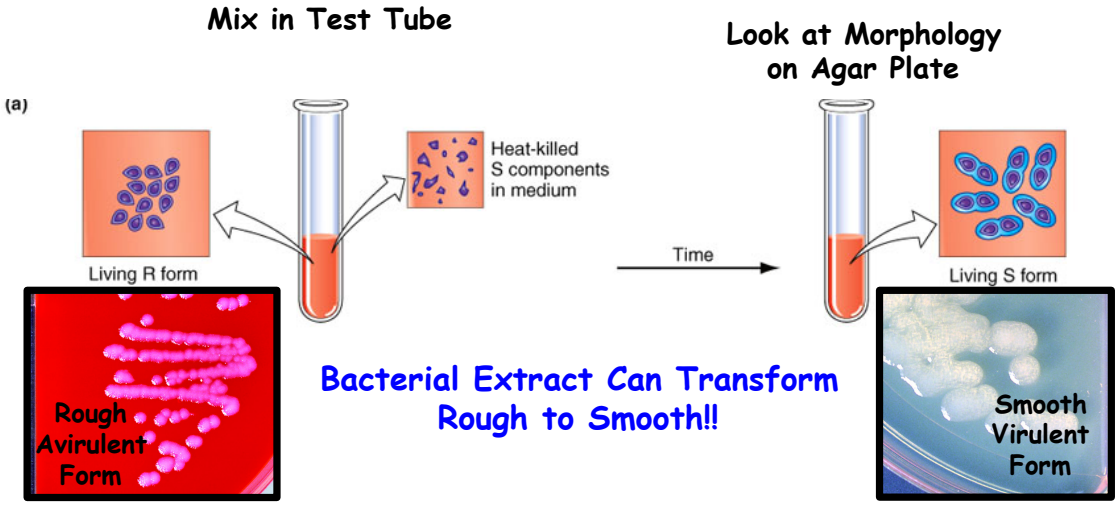
BY OSWALD T. AVERY, M.D., COLIN M. MACLEOD, M.D., AND MACLYN MCCARTY,* M.D.

Avery et al. Questions?

1. Does the Transforming Principle Come From the Mouse or Bacteria?
2. If From the Bacteria -- What Substance?
3. How Devise Techniques to Determine What is the Transforming Principle?
   a) Transformation in Test Tube
   b) Isolation of Macromolecules
   c) Isolation of Enzymes (e.g., DNase, RNase)

Design Experiments To Show!!!

Does the Transforming Principle Come From the Mouse or Bacteria?



Bacterial Extract Can Transform Rough to Smooth!!

Hypothesis? Predictions? Experiment?

What Are the Major Chemical Components of a Bacterial Cell?

What Could Be the Transforming Principle?

1. What is Predicted if DNA is the Genetic Material?

2. How Test Hypothesis?

Table 2–2 The Approximate Chemical Composition of a Bacterial Cell

	PERCENT OF TOTAL CELL WEIGHT	NUMBER OF TYPES OF EACH MOLECULE
Water	70	1
Inorganic ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	~300
Macromolecules (proteins, nucleic acids, and polysaccharides)	26	~3000

Macromolecules

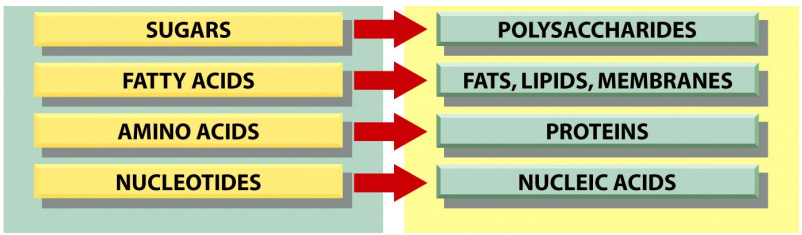
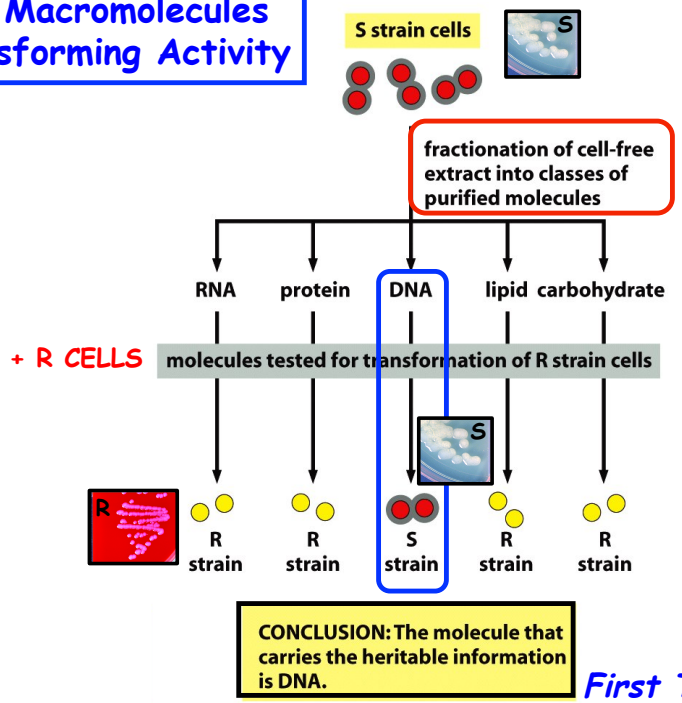


Table 2-2 *Molecular Biology of the Cell* (© Garland Science 2008)

Testing Macromolecules For Transforming Activity



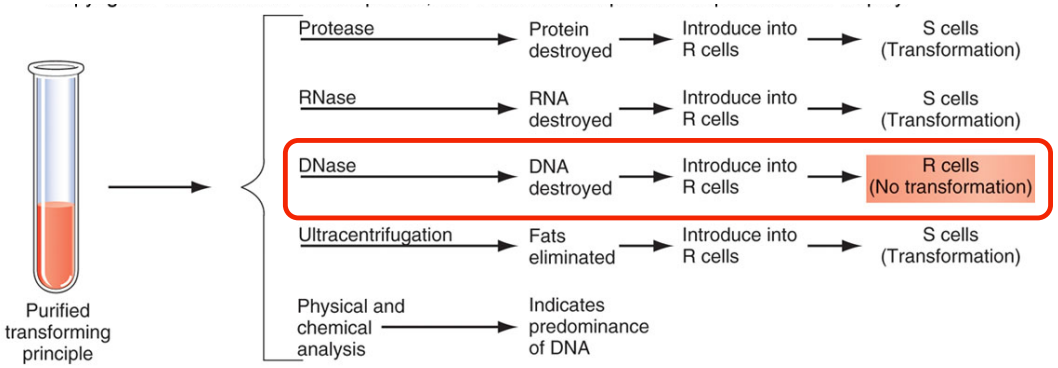
First Transformation Experiment With Purified Molecules!!

Figure 4-2 *Molecular Biology of the Cell* (© Garland Science 2008)

The Avery et al. Experiment Showed Conclusively that DNA is the Genetic Material?

a. yes
b. no

THE Critical Experiment by Avery et al.Showing That DNA IS THE Genetic Material

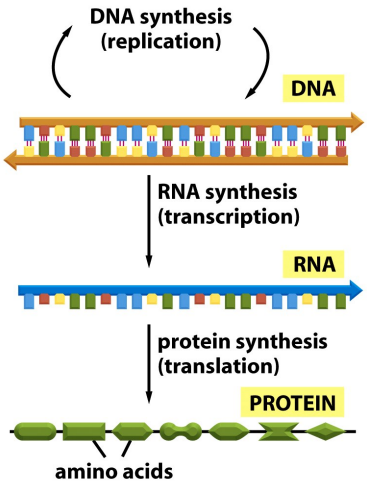


When DNase Destroyed DNA There Was No Transformation & Only Rough Cells Were Found in the Culture

If Smooth DNA Not Present, Rough Cells Cannot Be Transformed Into Smooth Cells!

How Did Avery et al. Experiments Verify the Hypothesis That DNA is the Genetic Material

Predictions	Results
Replication	Yes
Phenotype	Yes
Stable	Yes



Cell Processes

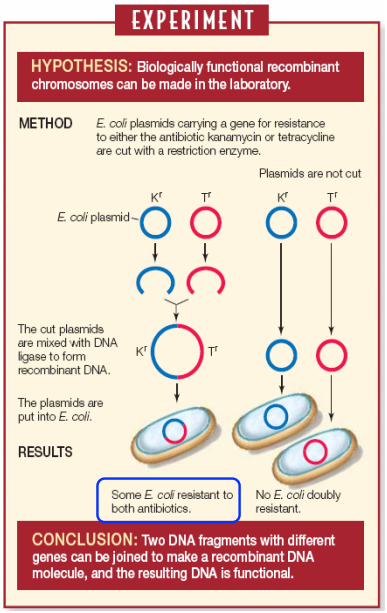
1. S DNA Taken Up By R-Cells
2. S Gene Transcribed Into S mRNA
3. S mRNA Translated Into Smooth Protein
4. Smooth Protein Helps Construct Sugar Capsule and Protects Bacteria From Antibodies ∴Cells Virulent

Transformation is a Basic Genetic Engineering Process Today!

Transformation=Ability of Cell Phenotype To Be Changed by DNA!

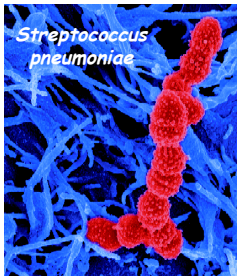
Can Bacteria Be Transformed With Other Genes and Traits?

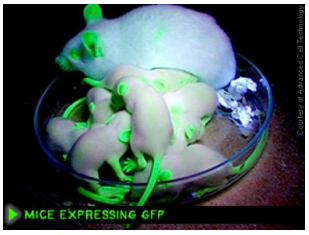
Cohen & Boyer Experiment That "Invented" Genetic Engineering

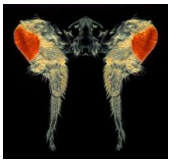


Because the Transforming Principle is DNA
Any Gene Can Be Transformed (e.g., Antibiotic^R to Antibiotic^S)

All Organisms Can Be Transformed!!
Genetic Engineering Has Come a Long Way Since Griffiths Experiments in 1928!!







Genetic Engineering/Transformation Involves Incorporating Engineered DNA or Genes Into Different Organisms

Genotype

Phenotype

Engineered Gene MUST

1. Enter Target Cell
2. Use Target Cell Machinery Enzymes to Become Part of Chromosome
3. Replicate with Target Cell Chromosome
4. Use Target Cell Protein Synthesis Machinery to Make a New Protein → Phenotype Trait!

Engineered Gene CAN BE

1. From Same Organism
2. From Different Organism
3. From a Combination of Organisms stitched together by Genetic Engineering

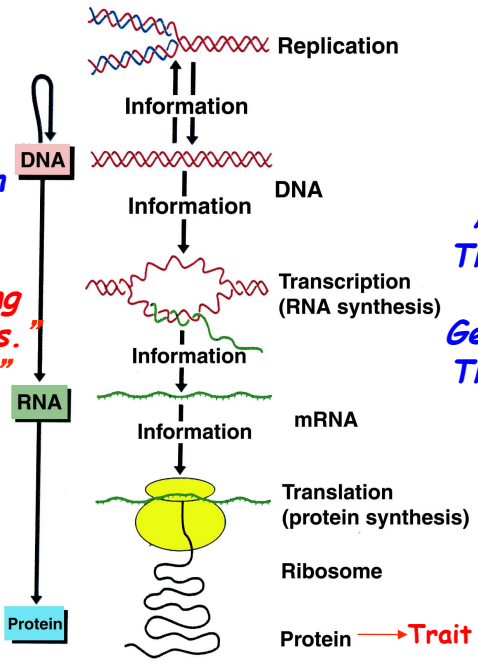
Gene Engineering Shows that Gene Processes Are Universal!!!

Just Like The GlowGene Experiments!!!

Transformation of Cells With DNA Uses Normal Cellular Processes To Produce a New Phenotype

Can Intervene in This Process in Cells

Genetic Engineering Is not "Hocus Pocus." It Uses "Natural" Cell Processes!!!!



All Organisms Use The SAME Processes And "RULES" to Generate Traits!! And The SAME Molecules & Chemistry!!

What is A Gene?

Begin 5'

```
TGAAAATCCAAAAAAATAGGA
GTTTGGTGTTTGGGTTTTAGG
TAGGAAATAATTTGGGTCTTT
TTTAGGTTTCGGGTTTGGGTT
ATTTGAGTGTTTGACATTTGA
AATTTCGGTGTTTCATCTTCG
TGGGTGTGCCAGTGGCGTGAG
TGTTCCCCGGTTTCGTCAACT
TACGGTTTAGGGTTTACCAAG
TTAGGGTTTAGGGTTTGAGAT
GGCGGCCATTTCTCATGTTTG
AAACAAAGCCTGAAAATCAAA
TGGGTGTGCCGGTGGCGTGAG
CGTTCCCCGGTTCCGTCAACT
ATCAAGTACCCATGTTTGGGA
TGAACGTCAATGAACACGAAA
AAAAAAATAGGAAATCGACCC
AGAAAAGGGAGGGTGGCCATT
ACTATCACGTAACAACAAAAC
ATTTTTTTGCGTGGGTGTGCC
ATAAATAGATTTTTCCCTTGT
CCTTTTCCATGTTCAAGTACC
TTTCTCATGTTTTGAAGTCAA
CCTGAAAATCCAAAAAAATAG
CAGTGGCGTGAGACATTGGAG
GATACGTCAACTAACACGTAA
CATGTTTGGGATTTTTTTCCG
AGAACCCAAAAAAAATAGTCT
GAAATCGACCCTTTTCCATGT
GGGCAGCCATTTCTCTTGTTT
AAAACAAAGCCTGAATATCTA
GTGAGTGTGCCAGTGGCGTGA
TCGTTCCCCGGTTCCTTCAAC
GTTCAAGTACCCATGTTTGGG
TTGGACGTCAAAGAAACCAAA
CAAAAAAATAGGAAATCGACC
AGAAAATGGAGGGCGGCCAAT
CTGACACGTAAAAACAAAGCT
TTTTTTCGCGTGGGTGTGCCA
AAAATAGTCCCGTTCCCCGTT
TTTTCCATGTTCAATTACCCA
TCTCATATTTGGACGTCAAAG
```

End 3'

Sequence or Order of Nucleotides Coding DNA Strand

The β-globin Gene

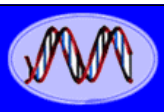
Blood Protein Carries Oxygen to All Genes From Lungs ⇨ Energy

A Gene is a Unique Sequence of Nucleotides Specifying a Function

DNA Sequence = Biology!
What If Sequence Changed?

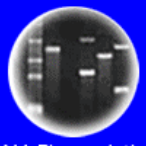
SEQUENCE → FUNCTION

Relative to Coding or Sense Strand of Gene



DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria



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Genes & Genomes Differ Because the Sequence of DNA Differs

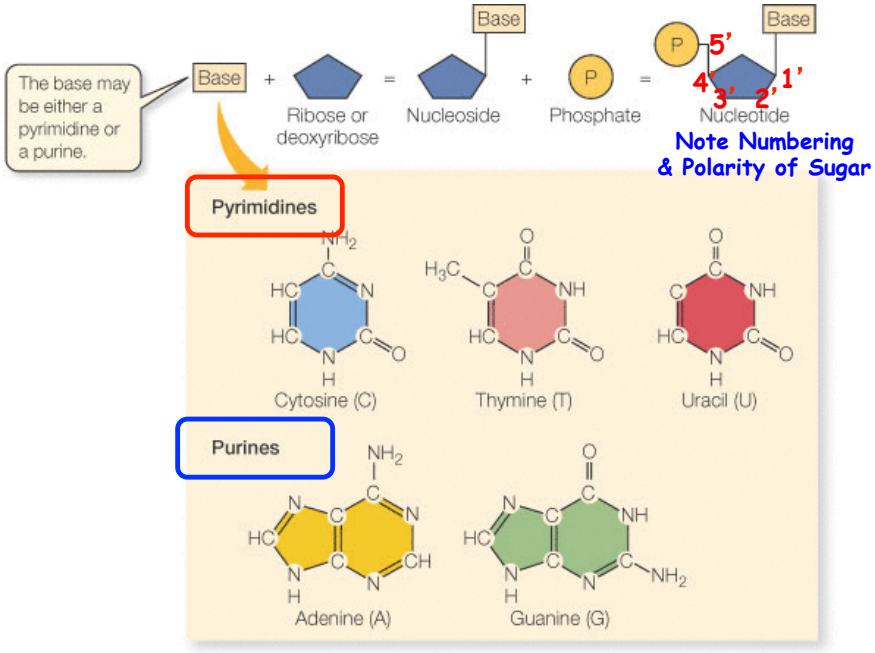
DNA Sequence
Beginning → End
5' 3'

→ Biological Uniqueness

If You Know the DNA Sequence, You Can Engineer Anything! Even Make New Genes & Genome!

Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

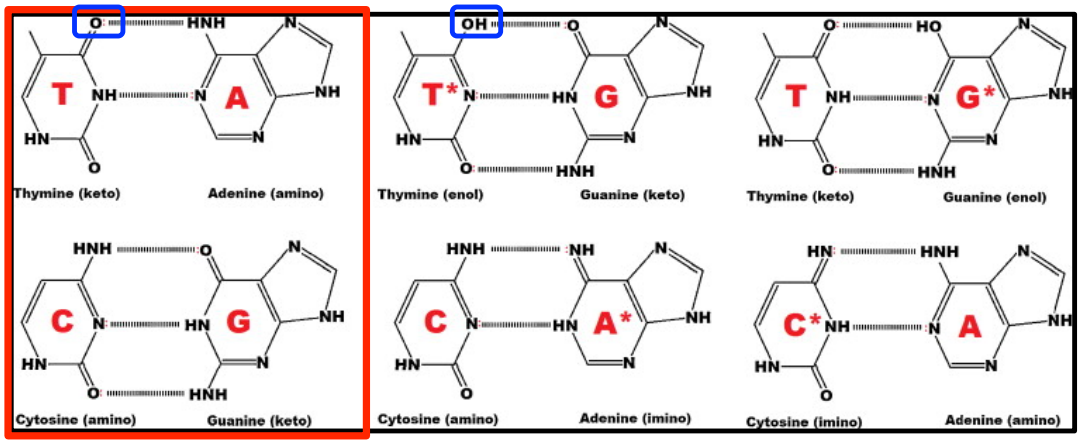
There Are Four Different Nucleotides in DNA



Note Chemical Differences in Bases -- Chemistry Leads to Biology!!

TAUTOMERS CHANEGE BASE PAIRING RULES

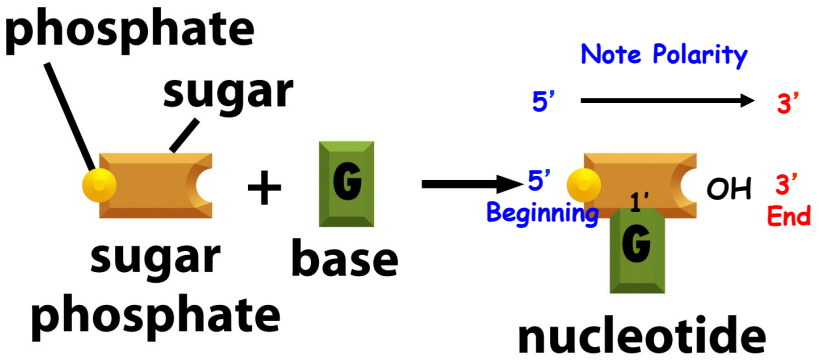
Normal Forms – Keto & Amino



And Lead To Mistakes in DNA Replication & Mutations ➤ Genetic Diversity

Chemistry Leads to Biology!!

Nucleotides Have Polarity
Based on What is Bonded to the Five-Carbon Sugar
Phosphate on 5' Carbon and OH on 3' Carbon



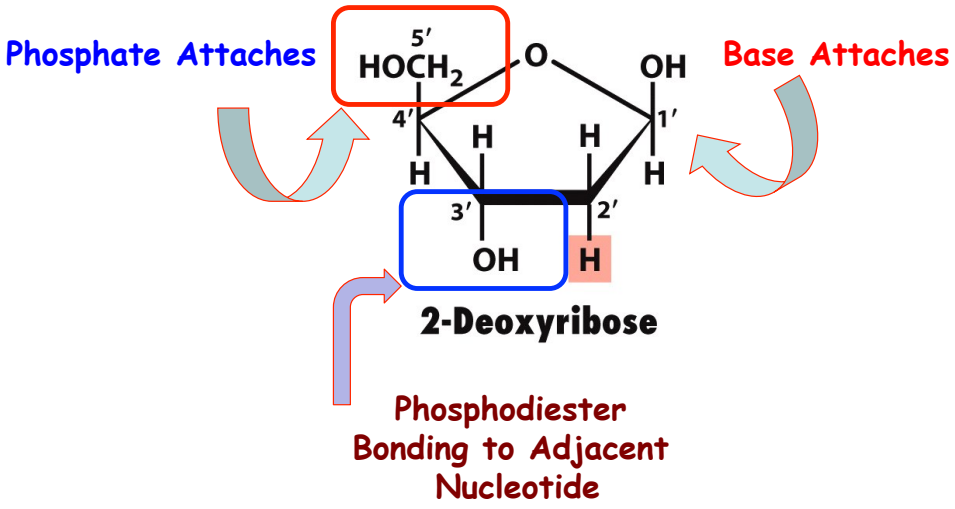
The Sugar is the HUB

DNA Sequence Defined By Nucleotide Order

DNA Sequence = Functional Uniqueness = Biology

Figure 1-2a *Molecular Biology of the Cell*, Fifth Edition (© Garland Science 2008)

Note Structure and Polarity of Deoxyribose Sugar



Nucleotides Are Joined By 5' to 3' Phosphodiester Bonds

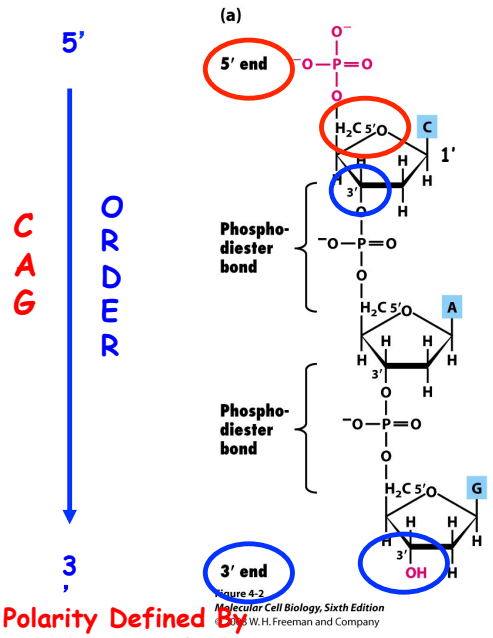


Figure 4-2
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

1. The Order is Specified by the Nucleotides That Join 5' to 3'
2. This is the Basis For All of Biology
3. Order is Maintained During DNA Replication
4. Basis of All Genetic Engineering

Polarity Defined By
Sugars & Order Specified By Bases

Clues to the Double Helix-Chargaff's Rules
Purines = Pyrimidines

TABLE 6.1 Chargaff's Data on Nucleotide Base Composition in the DNA of Various Organisms

	Percentage of Base in DNA				Ratios	
Organism	*A*	*T*	*G*	*C*	*A:T*	*G:C*
Staphylococcus afermentams	12.8	12.9	36.9	37.5	0.99	0.99
Escherichia coli	26.0	23.9	24.9	25.2	1.09	0.99
Yeast	31.3	32.9	18.7	17.1	0.95	1.09
*Caenorhabditis elegans**	31.2	29.1	19.3	20.5	1.07	0.96
*Arabadopsis thaliana**	29.1	29.7	20.5	20.7	0.98	0.99
Drosophila melanogaster	27.3	27.6	22.5	22.5	0.99	1.00
Honeybee	34.4	33.0	16.2	16.4	1.04	0.99
Mus musculus (mouse)	29.2	29.4	21.7	19.7	0.99	1.10
Human (liver)	30.7	31.2	19.3	18.8	0.98	1.03

*Data for *C. elegans* and *A. thaliana* are based on those for close relative organisms.
Note that even though the level of any one nucleotide is different in different organisms, the amount of A always approximately equals the amount of T, and the level of G is always similar to that of C. Moreover, as you can calculate for yourself, the total amount of purines (A plus G) nearly always equals the total amount of pyrimidines (C plus T).

What Would You Predict For a Single-Stranded DNA?

THE COMPOSITION OF THE DESOXYPENTOSE NUCLEIC ACIDS OF THYMUS AND SPLEEN*

BY ERWIN CHARGAFF, ERNST VISCHER,† RUTH DONIGER, CHARLOTTE GREEN, AND FERNANDA MISANI

J. Biological Chemistry, July, 1948

The New York Times

Obituaries

Erwin Chargaff, 96, Pioneer In DNA Chemical Research

By NICHOLAS WADE
Published: June 30, 2002

Erwin Chargaff, whose research into the chemical composition of DNA helped lay the groundwork for James Watson and Francis Crick's discovery of its double-helix structure -- the pivotal finding of 20th-century biology -- died on June 20 in a New York hospital. He was 96.

As a biochemist at Columbia University in the 1940's, Dr. Chargaff discovered regularities among the four chemical units of DNA known as bases, pointing directly to its role as the hereditary material of living organisms. But he was unable to interpret the meaning of his finding, a failure that allowed Dr. Watson and Dr. Crick to do so when they ascertained the structure of DNA.

Dr. Chargaff's data helped both in the two young scientists' discovery and even more in its acceptance by other scientists. "The base composition was an essential clue for finding the structure of DNA, there's no doubt about that," Dr. Watson said in an interview. "We could have come up with the answer, but no one would have believed it."

Dr. Chargaff later became a forceful if lonely critic of molecular biology, accusing its practitioners of "practicing biology without a license" when they learned to move genes from one organism to another.

A man of wide culture and learning, he did not fit easily into the sharply focused world of scientific specialists. Ever the European, he found much in American life to criticize, despite his long and productive tenure at Columbia. He cherished the outsider's role, modeling his sardonic view of the world on the writings of Karl Kraus, the Viennese satirist.

"I have not fitted well," Dr. Chargaff wrote in 1975, "into the country and the society in which I had to live; into the language in which I had to converse; yes, even into the century in which I was born."

Erwin Chargaff was born on Aug. 11, 1905, in Czernowitz, then a provincial capital of the Austrian monarchy. His father, Hermann, was a banker who later lost his business. Of his mother, Rosa Silberstein, he wrote that she died, "only God knows where and when, having been deported into nothingness from Vienna in 1943." He is survived by his only son, Thomas.

As a young man, Dr. Chargaff studied chemistry at the University of Vienna. He worked at the University of Berlin and then at the Pasteur Institute in Paris before arriving at Columbia University in 1935. After reading the 1944 report by Oswald Avery that identified DNA as the hereditary material, Dr. Chargaff switched his laboratory to the study of DNA and the four bases, or chemical groups, of which it is composed -- adenine, cytosine, guanine and thymine.

He soon noticed a striking regularity about the base composition of DNA: from whatever plant or animal he derived DNA, the amounts of adenine and thymine were almost the same, and so were the amounts of cytosine and guanine.

Dr. Chargaff published the result but made little progress in understanding the reason for the regularity, which is that adenine on one of the DNA molecule's two strands is always paired with thymine on the other, as is cytosine with guanine. But in a fateful and testy lunch in May 1952, he discussed his results with Dr. Watson and Mr. Crick (who did not yet have his doctorate).

"They impressed me by their extreme ignorance," he later told Horace Judson, the historian of the discovery of DNA. "They told me they wanted to construct a helix, a polynucleotide to rival Pauling's alpha helix. They talked so much about 'pitch' that I remember I wrote down afterwards, 'Two pitchmen in search of a helix.' "

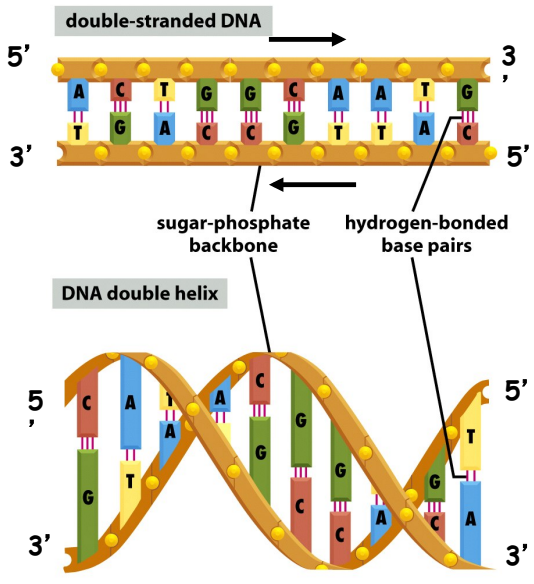
He later wrote that "I believe that the double-stranded model of DNA came about as a consequence of our conversation." Mr. Judson, however, in an appendix to a new edition of his book "The Eighth Day of Creation" (Cold Spring Harbor Press, 1996), concluded that Dr. Chargaff's claim was something of a stretch, since Dr. Watson and Dr. Crick had not at that time hit on the concept of base pairing, nor had Dr. Chargaff alluded to it in his publications.

Though Dr. Chargaff tended toward the sardonic, it was hard for observers to understand the depth of his bitterness in his attitude to his fellow scientists. The reason, besides his disappointment at having missed discovering the structure of DNA, was that he was pushed to the sidelines by Dr. Crick in the worldwide effort to interpret the structure.

"By 1958," Mr. Judson writes, "Dr. Chargaff was denouncing molecular biology and its practitioners for arrogance, ignorance, reductionism and self-serving sensationalism."

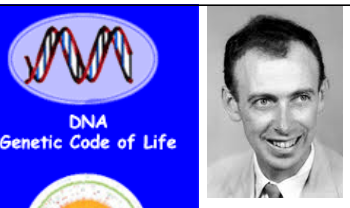
"The technology of genetic engineering poses a greater threat to the world than the advent of nuclear technology"

DNA is a Double Helix of Two Complementary Chains of DNA Wound Around Each Other



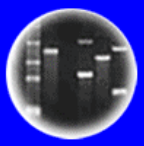
Watson and Crick, Nature, 1953

1. Complementary Strands
2. A=T and G=C (Four Bases)
3. Sequence of Strands Differ
4. Bases to Interior
5. Phosphate-Sugar Backbone on Exterior
6. DNA Strands in Opposite Direction (Only Way Helix Fits)
7. Sequence of One Chain Automatically Specifies Sequence of Complementary Chain (Basis of Replication!)
8. No Constraint on Sequence (4^n=n # sequences)
9. DNA has dimensions (Know # bp Know Length: 20Å diameter, 3.4Å/bp, 10bp/turn)
10. Sequence = Biology



DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria



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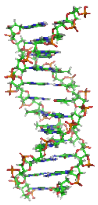
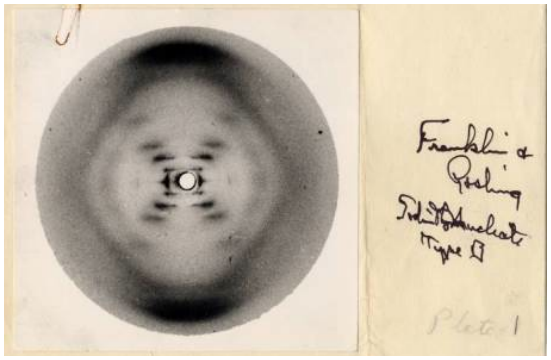
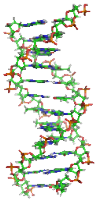
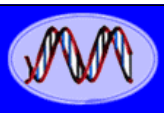
Reflections on The *"Race For the Double Helix"* Film









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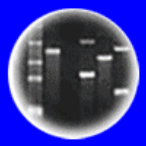

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MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

Nature, April 25, 1953

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. 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

DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria

DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

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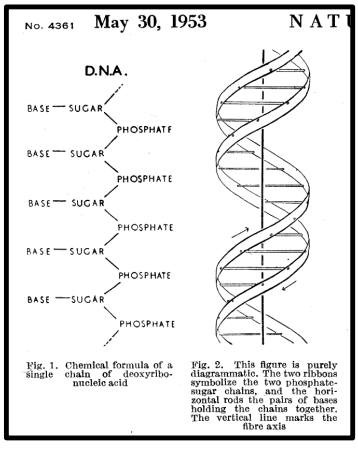
GENETICAL IMPLICATIONS OF THE STRUCTURE OF DEOXYRIBONUCLEIC ACID

By J. D. WATSON and F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge

Nature, May 30, 1953



No. 4361 May 30, 1953 N A T

D.N.A.

BASE — SUGAR — PHOSPHATE

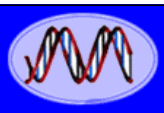
Fig. 1. Chemical formula of a single chain of deoxyribonucleic acid

Fig. 2. This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

Our model suggests possible explanations for a number of other phenomena. For example, spontaneous mutation may be due to a base occasionally occurring in one of its less likely tautomeric forms. Again, the pairing between homologous chromosomes at meiosis may depend on pairing between specific bases. We shall discuss these ideas in detail elsewhere.

For the moment, the general scheme we have proposed for the reproduction of deoxyribonucleic acid must be regarded as speculative. Even if it is correct, it is clear from what we have said that much remains to be discovered before the picture of genetic duplication can be described in detail. What are the polynucleotide precursors ? What makes the pair of chains unwind and separate ? What is the precise role of the protein ? Is the chromosome one long pair of deoxyribonucleic acid chains, or does it consist of patches of the acid joined together by protein ?

Despite these uncertainties we feel that our proposed structure for deoxyribonucleic acid may help to solve one of the fundamental biological problems—the molecular basis of the template needed for genetic replication. The hypothesis we are suggesting is that the template is the pattern of bases formed by one chain of the deoxyribonucleic acid and that the gene contains a complementary pair of such templates.



DNA
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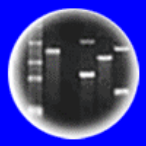

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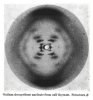
Molecular Structure of Deoxypentose Nucleic Acids

M. H. F. Wilkins
Medical Research Council Biophysics Research Unit,

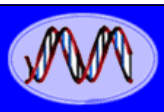
A. R. Stokes
H. R. Wilson
Wheatstone Physics Laboratory, King's College, London.
April 2. Nature, April 25, 1953

Molecular Configuration in Sodium Thymonucleate

Rosalind E. Franklin*
R. G. Gosling



Wheatstone Physics Laboratory, King's College, London.
April 2. Nature, April 25, 1953



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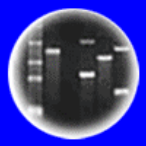

DNA Fingerprinting

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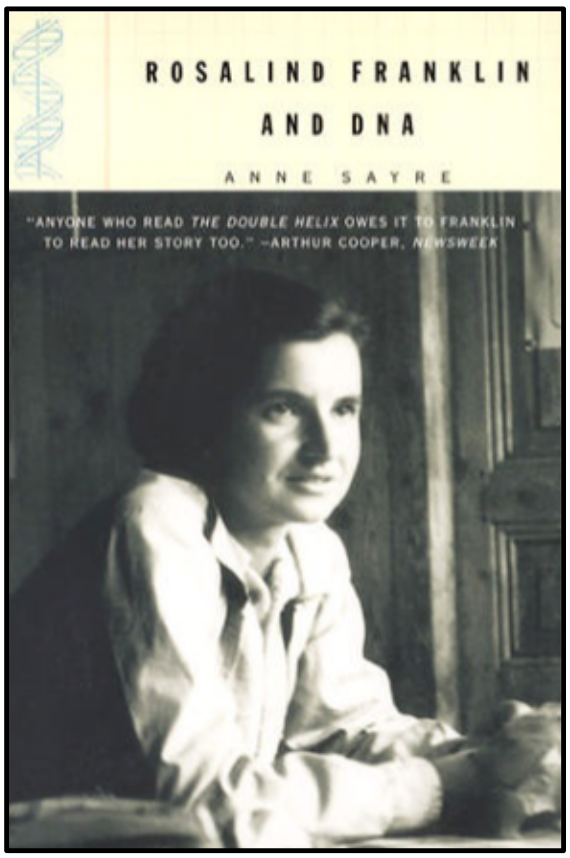
If You Were on the Nobel Prize Committee, Who Would Be Your Choice(s) For Being Awarded the Nobel Prize For Discovering the Structure of DNA?

a. Watson
b. Crick
c. Wilkins
d. Franklin
e. Gosling
f. Chargaff

Note: Nobel Prize Rules Allow Only Three People To Share a Prize



ISBN
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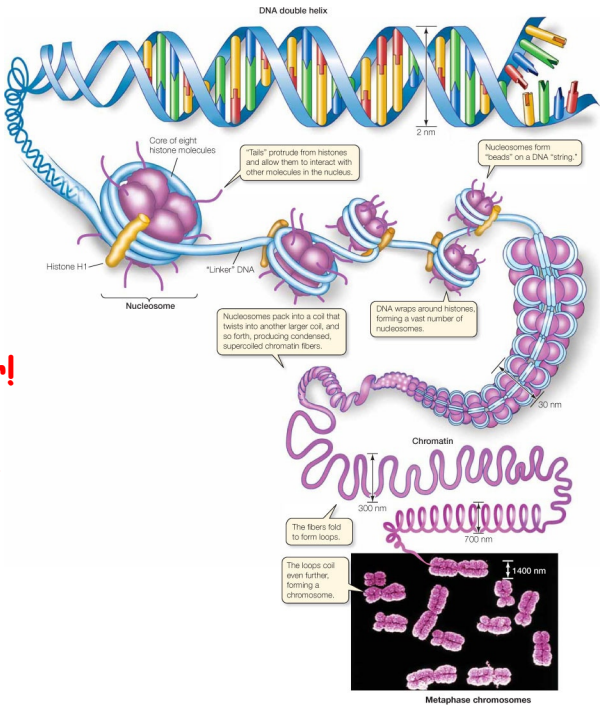
1975

A Chromosome Contains One (or Two!!) Continuous DNA Molecule(s)

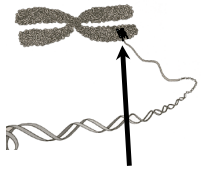
DNA in Human & Eukaryotic Chromosomes is Linear!

DNA in Most Bacteria is Circular!



A Chromosome Contains Many Genes Operating Independently

What is the Evidence?

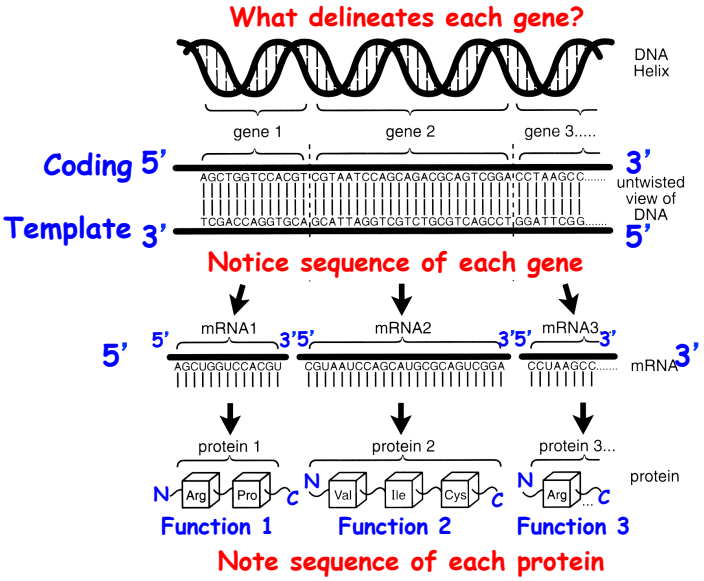


Position of Genes 1, 2, & 3 in chromosome

Discrete Units!

Notice- Each gene, mRNA, & protein has a unique order/ sequence of monomeric units

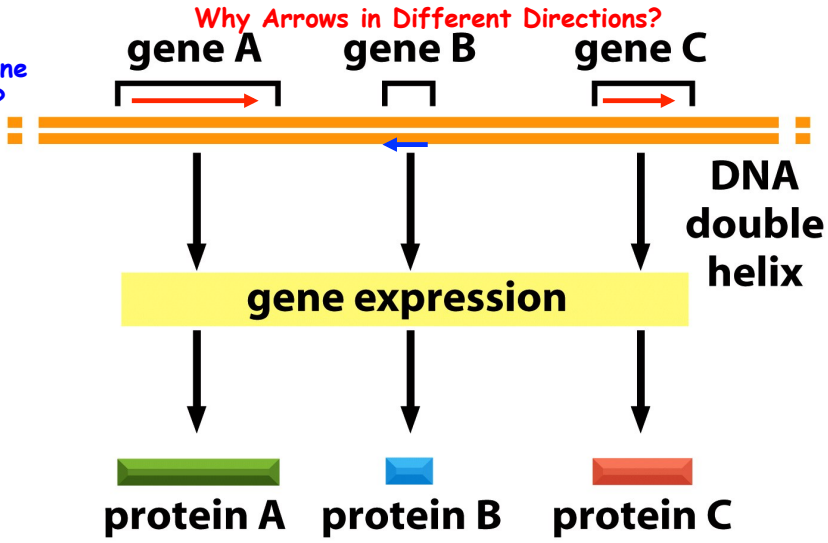
Central Dogma
∴Genes -> Functions in Cells via Proteins
Cells duplicate & stay the same -> DNA replication



VERY IMPORTANT CONCEPT!
COLINEARITY BETWEEN GENE SEQUENCE AND PROTEIN SEQUENCE

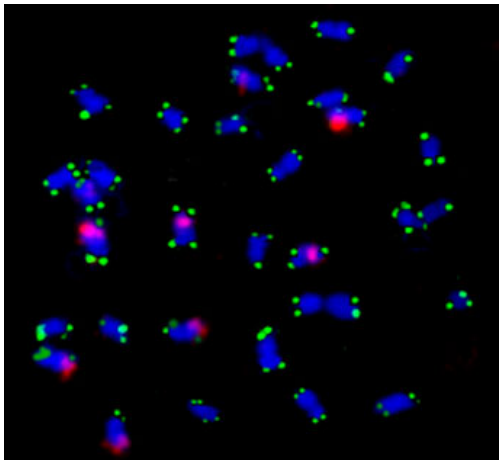
A Chromosome Contains Many Genes That Reside at Specific Positions and Have Unique Functions

What Defines Gene Positions?



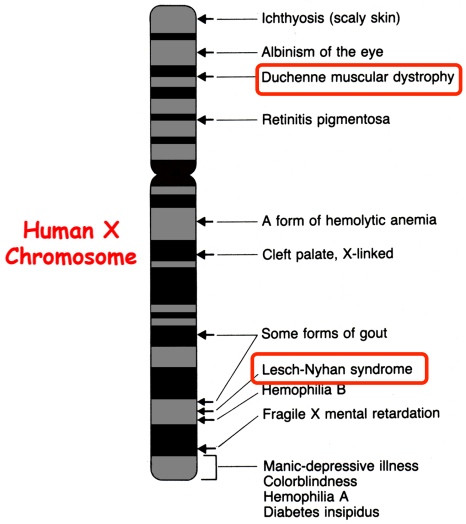
Because DNA Contains Two Strands--Genes Can Be Transcribed From Either Strand--But Only One Per Gene

Genes Reside at Specific Positions or Loci



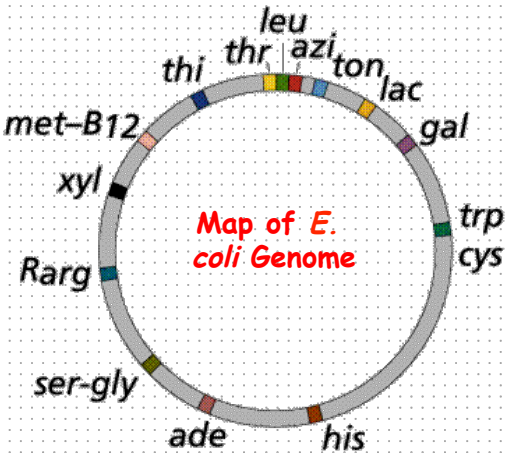
Gene Position = Locus = Unique DNA Sequence

Genes Reside at Specific Locations That Can Be Mapped



Human X Chromosome

Linear DNA
How Know?



Circular DNA
How Know?

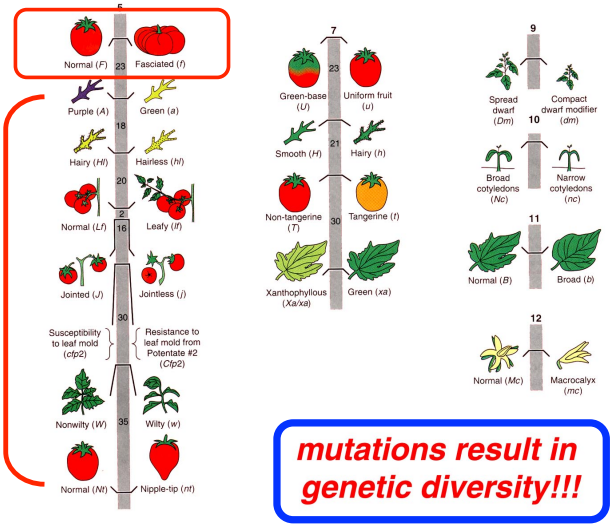
- Note Marker Bands - What are these? How are they useful?
- How Determine Gene Positions? Chromosome Number?

Alleles Reside at the Same Position on a Chromosome

Allele Phenotypes Specify Markers For Each Gene Location!

Alleles

Different Genes

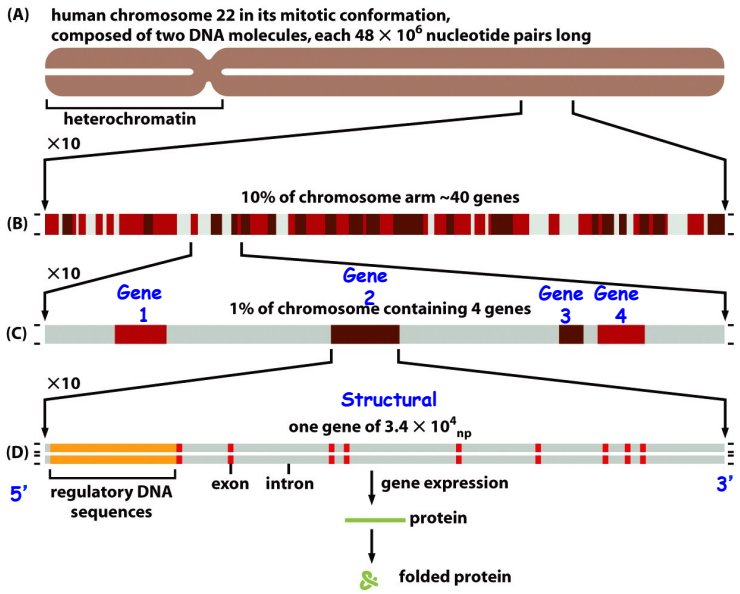


Gene Engineering Can Generate New Forms of Alleles of a Gene and, therefore, Results in More Genetic Diversity

mutations result in genetic diversity!!!

Alleles Are Different Forms of the Same Gene That Arise By Mutation & Can be Made in a Laboratory By Modern Genetic Engineering!

Organization of Genes on Human Chromosome 22



250 genes

Genes Are Defined/ Precise Regions of DNA

One Large Gene!

Genes Act As Individual Units?
How Know? GloFish Experiment! Genetic Engineering Antibiotic^R

Figure 4-15 *Molecular Biology of the Cell* (© Garland Science 2008)

A Conceptualized Gene

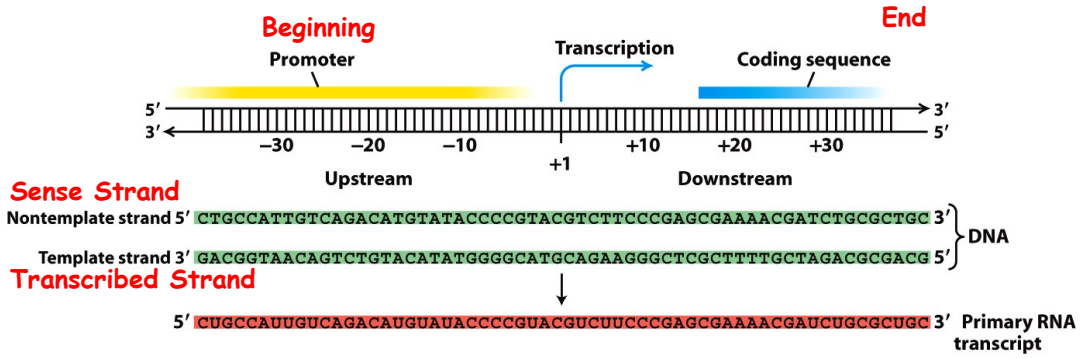
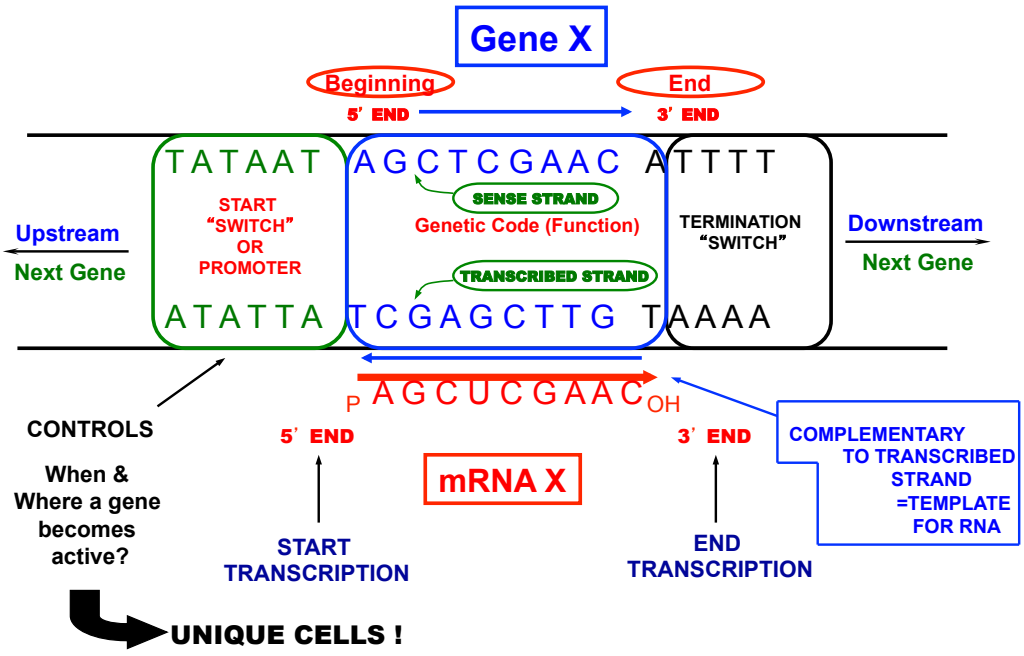


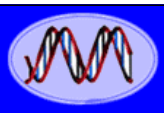
Figure 4-10b
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Recall -- *"Making Proteins in Recombinant Bacteria"* Article by Gilbert

A Gene is a Specific DNA Sequence That Directs the Expression of a Unique Trait



Note: mRNA Sequence = Sense Strand Sequence



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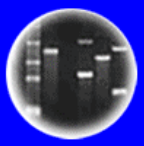

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A "Simple" Gene Reviewed

1. Sense Strand = Genetic Code
2. Sense Strand = 5' → 3' Direction (all DNA sequences specified 5' → 3')
3. AntiSense Strand = Complement of Sense Strand & is Transcribed Strand
4. mRNA = Same Sequence As Sense Strand & Complementary to AntiSense Strand
5. mRNA = 5' → 3'
6. Switch Turns Gene On - Not Transcribed But Upstream of Coding Region

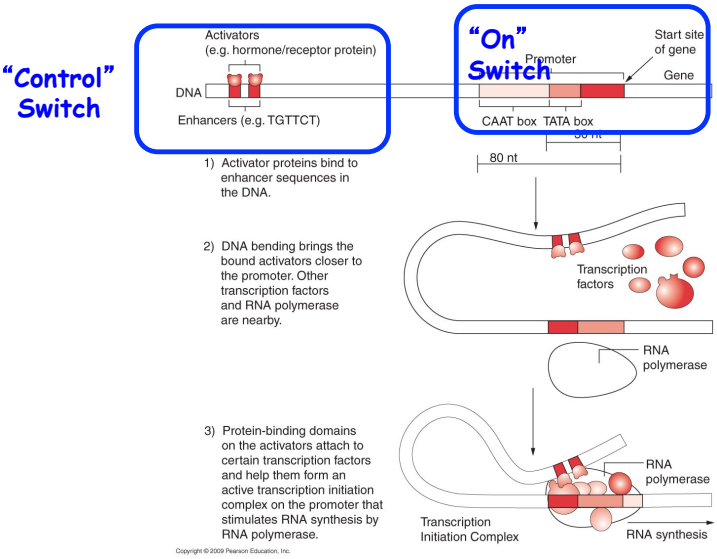
Genes Function As Independent Units! How Know? Design Experiment to Show!

"Everything" Follows the Double Helix & Its Rules - Anti-parallel Chains & Complementary Base Pairing!

Control Switches Are Unique DNA Sequences & Can Be Cloned

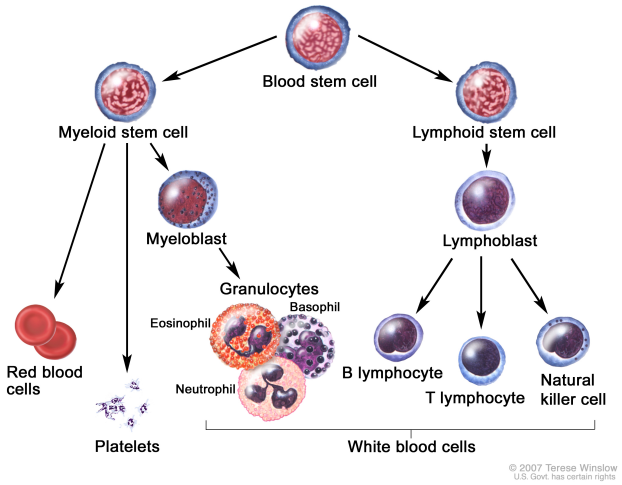
AND used to Re-Engineer Organisms!! Switches Act Independently of Gene!!

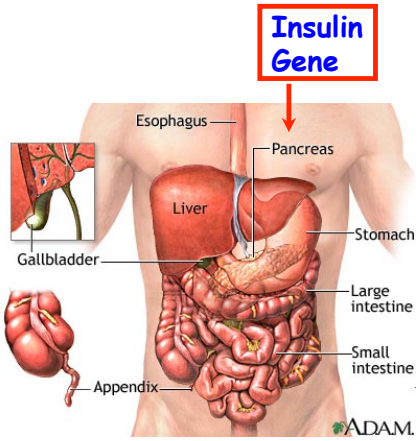
"Control" Switch

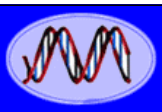


1. Each Switch Has a Unique DNA Sequence
2. Genome Projects Reveal Genes & Logic Controlled by the Switches
3. Sequence = Biology
4. No Hocus Pocus
5. Yo! It's in the DNA!!

Switches Control Where & When A Gene Is Active → Unique Functions → Unique Cells







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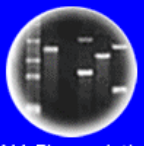

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THE GENE AND SWITCHES ARE UNIQUE DNA SEQUENCES

1. They Can Be Cloned & "Shuffled" & Engineered Creating New Genes That Have No Counterparts in Nature. ⇨ **Genetic Engineering**
2. These New Genes Can Be Transcribed in New Cell Types (Switch Change) &/or Organisms &/or Both. (e.g., Human Genes in Plant Leaves)

   ⇩

   Human Genes + Plant Leaf Switch
3. All Genes are Regulated & Controlled by Switches. Genome Projects Reveal Both the Genes & the Switches & Wiring Together of All Switches in Gene. ⇨ Program of Life From Birth to Death

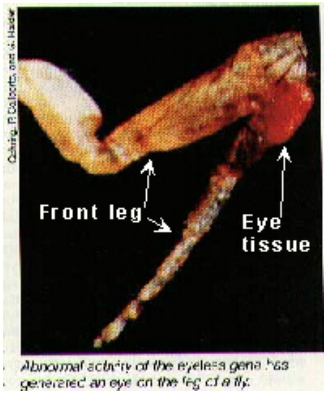
Yo! It's in the Sequences!!

The Eye Gene Can Be Expressed in Different Parts of the Fly by Engineering the Eye Switch

Eye Gene

Replace the Head Switch With the Leg Switch by Genetic Engineering

Eye Gene
+
Leg Switch



Abnormal activity of the eyeless gene has generated an eye on the leg of a fly.

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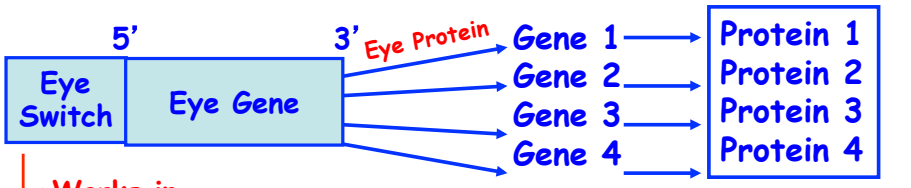
Eye Regulatory Network

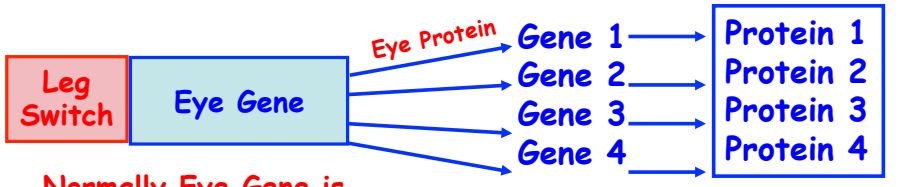
Control Genes Like The Eye Gene Control The Activity of Other Genes!



Works in Head!

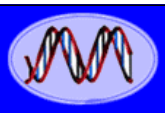
Eye Protein Binds to Switches to Turn Genes On!

Eye on Head!



Normally Eye Gene is OFF in Leg. Switch only Works in Leg.

Eye on Leg!



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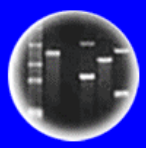

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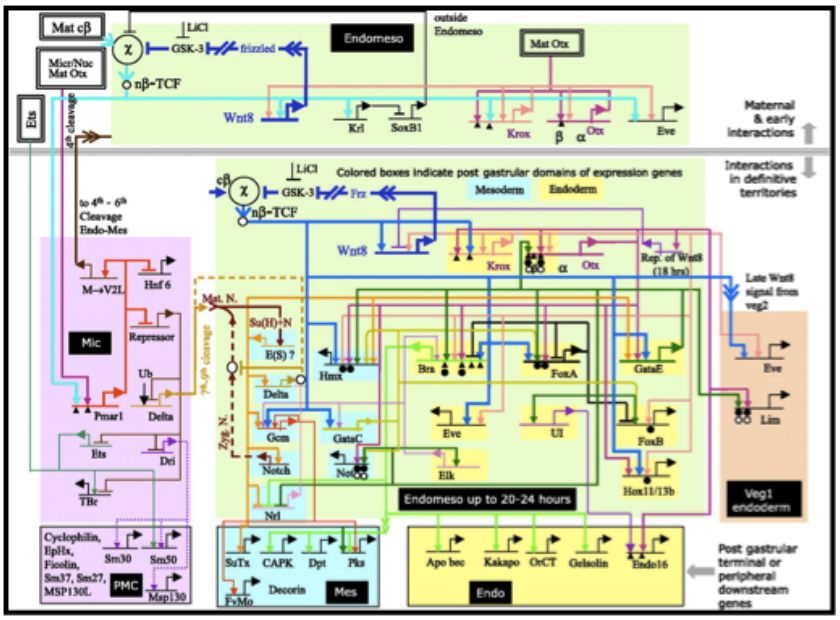
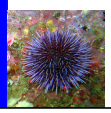
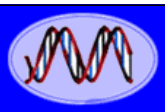
Ultimate Goal: To Dissect Genetic Regulatory Networks Programming Human Development From Birth to Death!





Genetic Networks Programming Early Sea Urchin Development



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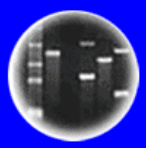

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100 Years Into The Future

1. If the Entire Human Genome is Sequenced?
2. If the Function/Protein of All Genes Are Known?
3. If All the Switches Are Identified & How They Go On & Off From Birth to Death?
4. If We Understand How Genes Are Choreographed & All the Sequences That Program them

What Does the Future Hold?

We Will Know at the DNA Level What Biological Information Programs Life to Death!

What Does This Mean For The Future of Humanity?

Remember - Mendel's Law Were Only Rediscovered 100 Years Ago & Look What We Can Do & Now!