One Gene- One Enzyme Theory

How Protein Synthesis came to be recognized as the Central Dogma of Molecular Genetics

The Central Dogma of Molecular Genetics

DNA

- Replication – in the nucleus

RNA

- Transcription- prod. In the nucleus- travels to cytoplasm

Protein

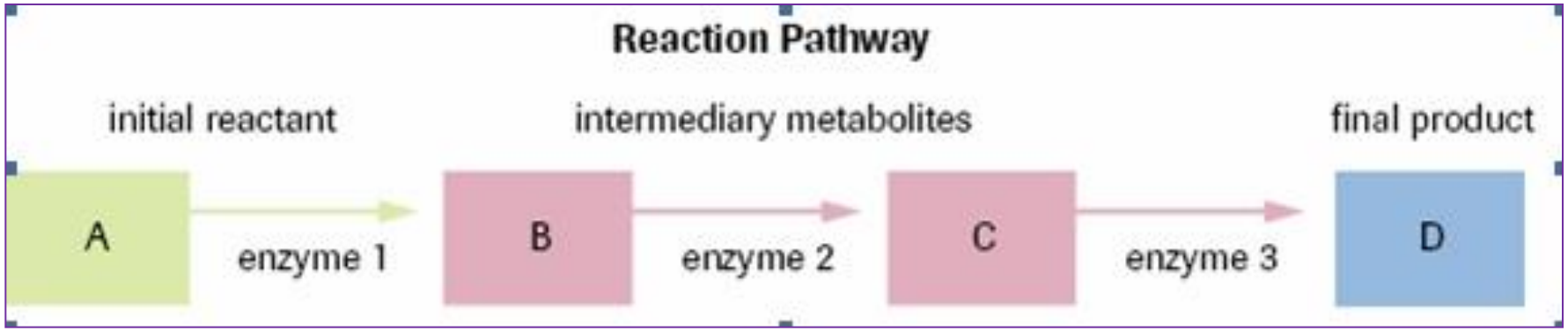
- Translation- occurs in the cytoplasm

Garrod's Hypothesis

In 1902, **Archibald Garrod** published a study linking genes and proteins.

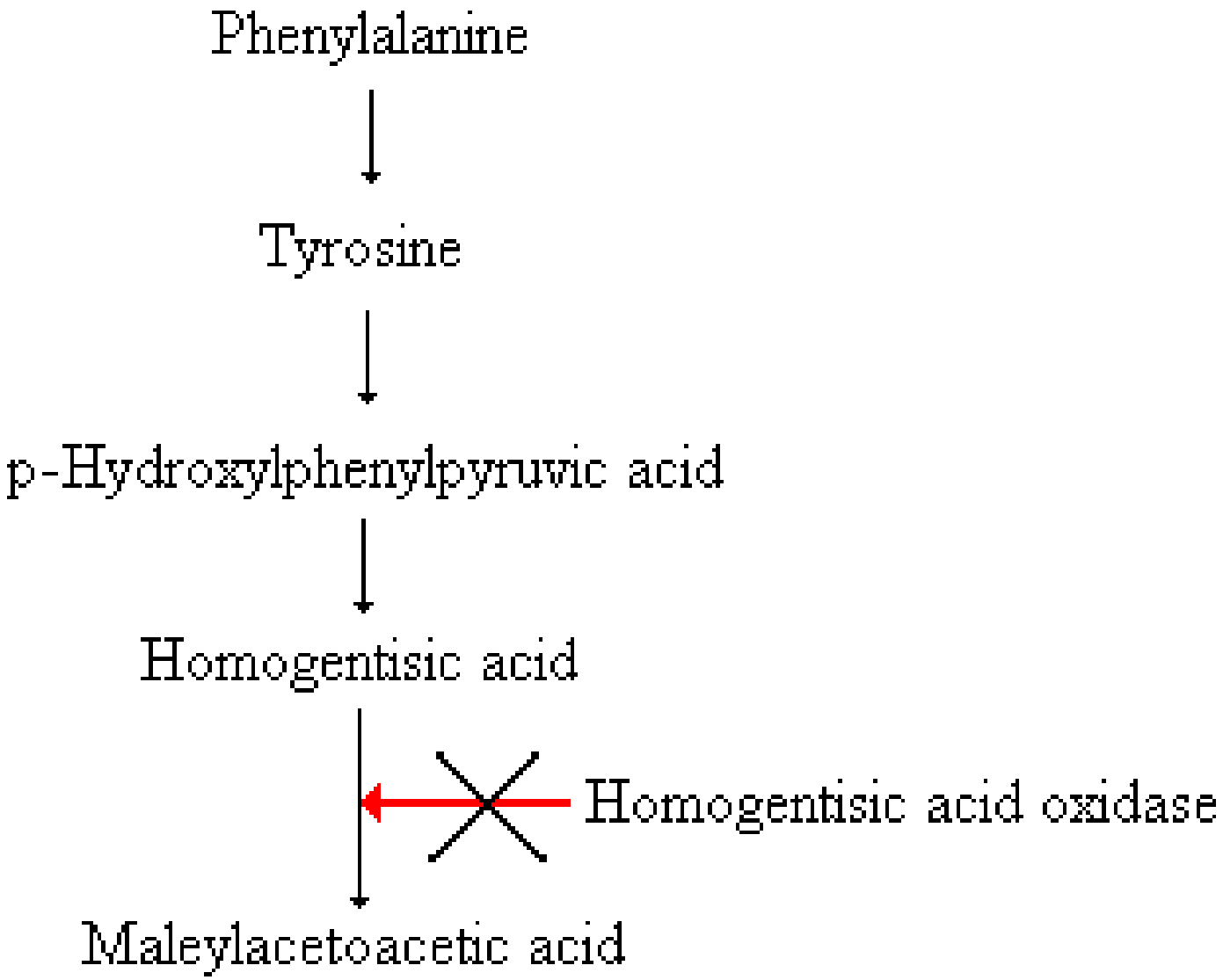
- studied the disease alkaptonuria and hypothesized that a defective enzyme caused an "inborn error of metabolism" along a reaction pathway

If there is an accumulation of Substance B then enzyme 2 must be defective.



The disease *alcaptonuria* causes a patient's urine to turn black when it is exposed to air.
This colour change is due to the build-up of homogentisic acid, an intermediate molecule produced during the catabolism of the amino acid phenylalanine.

Pathway:


Phenylalanine
Tyrosine
p-Hydroxylphenylpyruvic acid
Homogentisic acid
Homogentisic acid oxidase
Maleylacetoacetic acid

He reached the conclusions:

- Disease caused by a recessive inheritance factor.
- Having this factor would result in the production of the defective enzyme.
- This conclusion laid the foundations for demonstrating a link between genes and proteins.

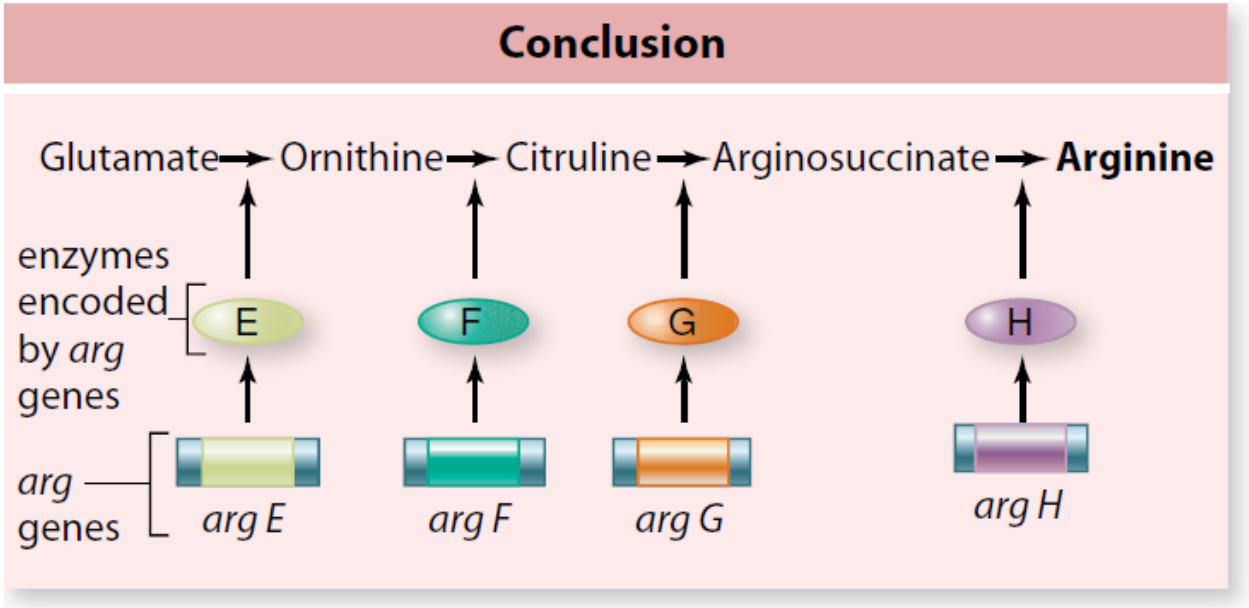
Beadle and Tatum

- 33 years later, they worked with bread mold *Neurospora crassa* & exposed spores to x-rays to create mutant strains. Through their experiments they concluded: a gene acts by directing the production of **only one** enzyme - called the one gene-one enzyme hypothesis.

- In 1941
- They used the bread mold *Neurospora crassa* to investigate whether one gene controlled the production of one enzyme or multiple enzymes.
- Normal, wild-type *N. crassa* can grow on minimal medium.

One-Gene/One-Polypeptide Hypothesis

Beadle and Tatum concluded that one gene codes for one enzyme. This relationship was updated to the **one-gene/one-polypeptide hypothesis**, since not all proteins are enzymes.



Vernon Ingram

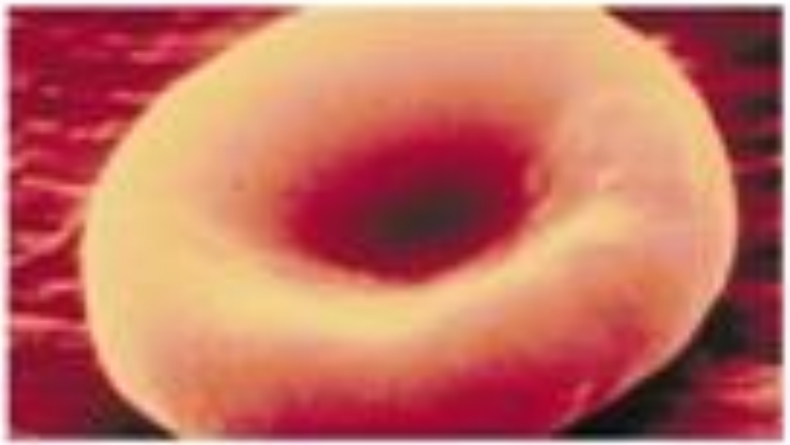
- by using Beadle and Tatum's work, he showed that sickle cell anemia results from alteration of a single gene . Many hereditary diseases have been traced to this type of alteration in just one gene.

normal hemoglobin β-chain

valine	histidine	leucine	threonine	proline	glutamic acid	glutamic acid

sickle cell anemia hemoglobin β-chain

valine	histidine	leucine	threonine	proline	valine	glutamic acid



Pathways

Most often the final product of the biochemical pathway is something essential to life, like amino acids, nucleotides, etc.

Finding a Messenger between DNA and Proteins

- In 1953, Frederick Sanger showed that each protein had a specific amino acid sequence.
- In 1961, François Jacob and Jacques Monod hypothesized that a special type of RNA, called **messenger RNA** (mRNA), is synthesized from DNA.
- Messenger RNA is complementary to DNA and provides the amino acid sequence information for protein synthesis.

The Genetic Code

The **genetic code** is a set of rules for determining how genetic information in the form of a nucleotide sequence is converted to an amino acid sequence of a protein.

Researchers identified four nucleotides in RNA (A, U, G, and C) and 20 amino acids. Mathematically, there could not be a one-to-one relationship between nucleotides and amino acids, nor could there be just two nucleotides per amino acid.

The **triplet hypothesis** states that the genetic code consists of a combination of three nucleotides, called a *codon*. Each codon would code for an amino acid. This hypothesis was supported by work done by Francis Crick and Sydney Brenner, which showed that the code is read in triplets.

Continued…

The Genetic Code

The nucleotide coding sequence from the wild-type virus is represented by the following hypothetical DNA sequence: CAG—CAG—CAG—CAG—CAG	**Result:** • Normal viral gene • Functional viral protein • Virus kills bacteria
1. The insertion or deletion of a single nucleotide or pair of nucleotides alters all subsequent nucleotide triplets. TCA—GCA—GCA—GCA—GCA T inserted at the beginning of the sequence.	**Result:** • The entire sequence is shifted to the right, causing each three-base segment to be altered from the original sequence. • Severe mutation in viral gene • Non-functional viral protein • Normal growth of bacteria
2. The insertion or deletion of two nucleotides has the same effect. TTC— AGC—AGC—AGC—AGC Two T's inserted at the beginning of the sequence.	
3. The insertion or deletion of three nucleotides alters at most two "words" of the code, after which the normal coding resumes. CAG—TTT—CAG—CAG—CAG CAT—TTG—CAG—CAG—CAG CTT—TAG—CAG—CAG—CAG Three T's inserted in various positions within the sequence.	**Result:** • The virus manufactures a modified version of the polypeptide, which is still partially functional. • Minor mutation in viral gene • Functional viral protein • Virus kills bacteria

Determining the Genetic Code

Between 1961 and 1965, researchers compared artificially synthesized RNA of known nucleotide sequences with the amino acid sequences of polypeptid
their corres

Table 6.1 The Genetic Code

First Base	Second Base				Third Base
	U	C	A	G	
U	UUU phenylalanine UUC phenylalanine UUA leucine UUG leucine	UCU serine UCC serine UCA serine UCG serine	UAU tyrosine UAC tyrosine UAA stop** UAG stop**	UGU cysteine UGC cysteine UGA stop** UGG tryptophan	U C A G
C	CUU leucine CUC leucine CUA leucine CUG leucine	CCU proline CCC proline CCA proline CCG proline	CAU histidine CAC histidine CAA glutamine CAG glutamine	CGU arginine CGC arginine CGA arginine CGG arginine	U C A G
A	AUU isoleucine AUC isoleucine AUA isoleucine AUG methionine*	ACU threonine ACC threonine ACA threonine ACG threonine	AAU asparagine AAC asparagine AAA lysine AAG lysine	AGU serine AGC serine AGA arginine AGG arginine	U C A G
G	GUU valine GUC valine GUA valine GUG valine	GCU alanine GCC alanine GCA alanine GCG alanine	GAU aspartate GAC aspartate GAA glutamate GAG glutamate	GGU glycine GGC glycine GGA glycine GGG glycine	U C A G

*AUG is an initiator codo
It also codes for the amin
acid methionine.
** UAA, UAG, and UGA
are terminator codons.

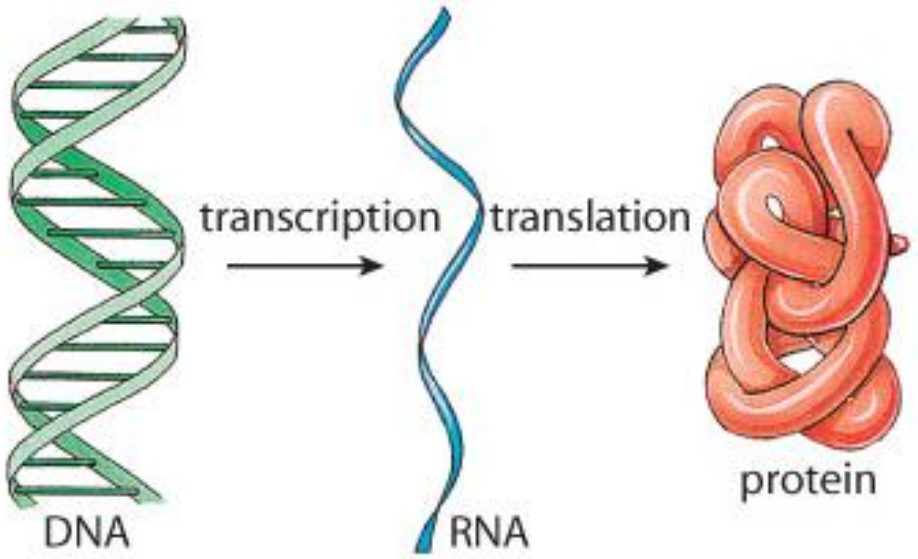
Summarizing the Genetic Code

The genetic code has three important characteristics. It is:

- redundant: more than one codon can code for the same amino acid
- continuous: the code is read as a series of three-letter codons
- universal: almost all organisms build proteins with the same genetic code. For example, a codon in a fruit fly codes for the same amino acid as in a human.

Gene Expression

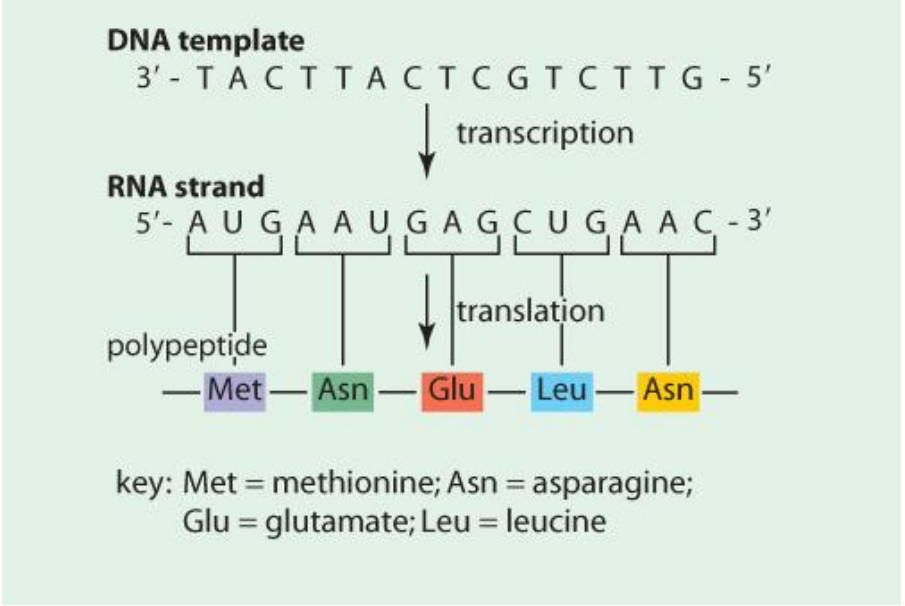
Gene expression refers to the transfer of genetic information from DNA to RNA to protein. This theory is called the *central dogma*



Gene Expression

The two steps in gene expression are transcription and translation.

- In **transcription**, a DNA sequence serves as a template for the synthesis of RNA.
- In **translation**, an mRNA sequence serves as a template for the synthesis of a protein.



Transcription of a DNA template produces an RNA molecule that is a copy of the genetic information. The nucleotide sequence of this RNA molecule is then translated using the genetic code so that the protein coded for by the gene is produced.