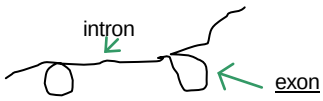
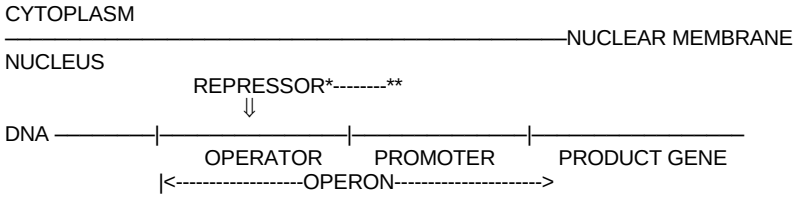
III.B - GENETIC CONTROL OF CELL FUNCTION, INHERITANCE & GENETIC DISORDERS

B.a. GENETIC CONTROL OF CELL FUNCTION

1) Gene [length of DNA responsible for a mean of 3 proteins]
2) Operon [length of DNA responsible for activity of several functionally-related genes]
3) Genome [all the different genes in a cell (body)] (many in a given cell inactive)
4) Introns & exons (in an entire DNA molecule, only exons are transcribed into m-RNA)



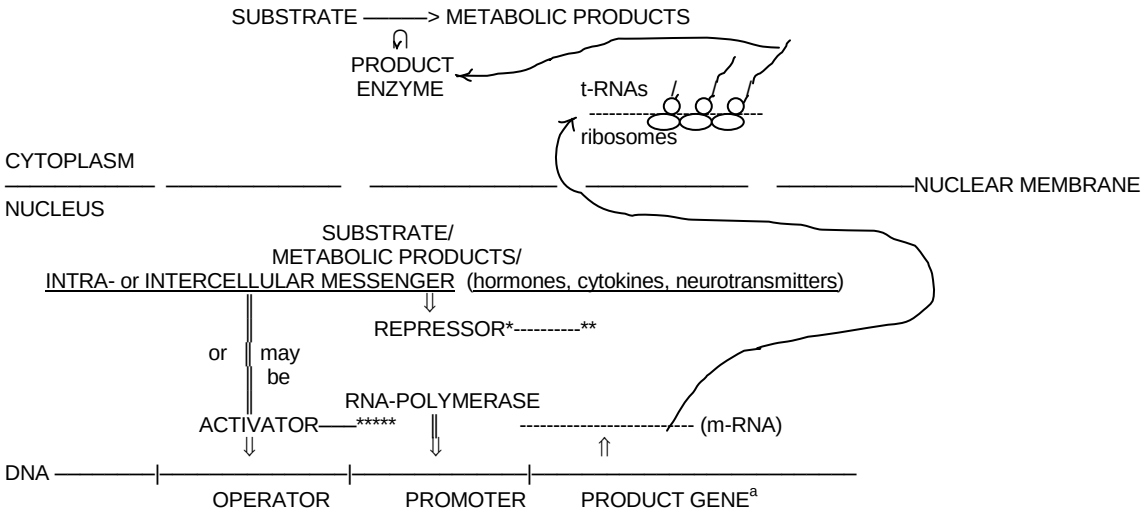
KEY: ⇓ = binds to



**REPRESSOR has a domain that extends over the PROMOTER & prohibits RNA-polymerase from binding to it or if it does bind to it, from initiating transcription of product gene.

Figure IIIB-1. The Configuration of an Inactive Inducible Gene TP IIIB-1

KEY: ⇓ = binds to
⇑ = transcription



*****ACTIVATOR includes a domain that extends into the PROMOTER & enhances the binding of RNA-polymerase to the PROMOTER.
*REPRESSOR is probably the activator for its own PROMOTER/PRODUCT-GENE
[a]PRODUCT GENE may include sequence for ACTIVATOR.

Critical Figure IIIB-2. The Configuration of an Active Inducible Gene TP IIIB-1

B.b. INHERITANCE
B.b.A. CHROMOSOMES

1) Chromatin [the unwound DNA molecules in a cell when they are making proteins]
2) Chromosome [a tightly-wound macromolecule made of a single molecule of DNA & protein] (Ch's exist in pairs)
3) Human Karyo\type {G nucleus,nut\} [22 pairs of autosomes & 1 pair of sex chromosomes: XX = ♀; XY = ♂]

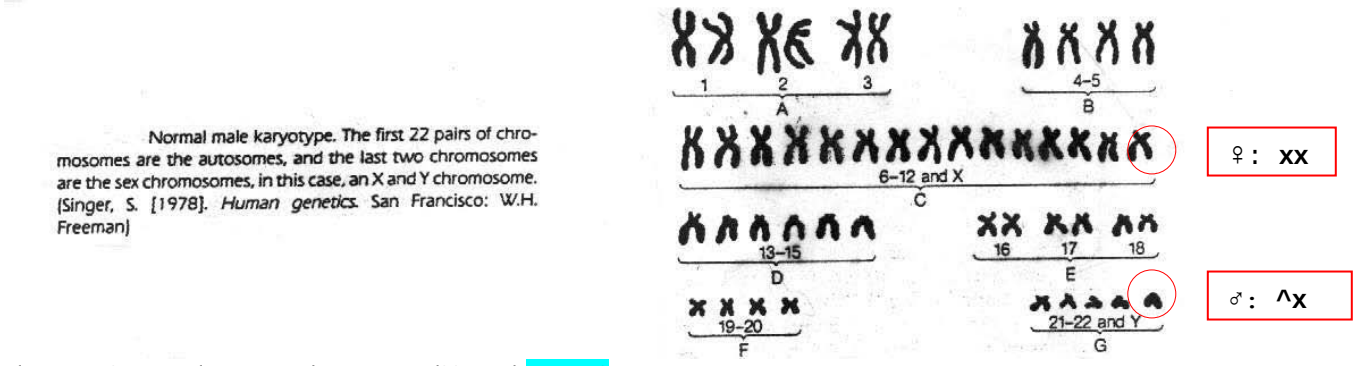


Figure IIIB-3. Normal Human Male Karyotype (32, p 47) TP IIIB-2

B.b.B. MEIOSIS, FERTILIZATION & MITOSIS

46 chromosomes as:
23 pairs of homologous chromosomes (homologues): { 2N dip\loid {G two\G form} —meiosis—> 1N hap\loid {G single\} ∴ N=23 in humans
(46) (23)

spermatogonium/ oogonium (23 23) (46) —(meiosis)—> 4 gametes (23) + (23) + (23) + (23) —{fertilization [+23]}—> zygote (23 23) (46) —(mitosis)—> adult (23 23) (46) 1

Figure IIIB-4. Concepts Relevant to Mitosis, Meiosis & Fertilization TP IIIB-3

1) Locus [position on chromosome where (product) gene is found] (Sci Am '96 46:198: ~ 256 genes necessary for prokaryotic cell, all others for specialization)
2) Allele [a form of the gene that produces a different product from other forms] (because chromosomes are paired, most genes occur in pairs. It is conceivable, therefore, that an individual could carry two different alleles for that gene; but most genes have only one allele. Some have a few alleles, w 1 being abundant in the population & the others being rare. In a very few genes, there are many alleles in the population, many of which occur in an appreciable proportion: polymorphism (8, p 79), Human Genome Project

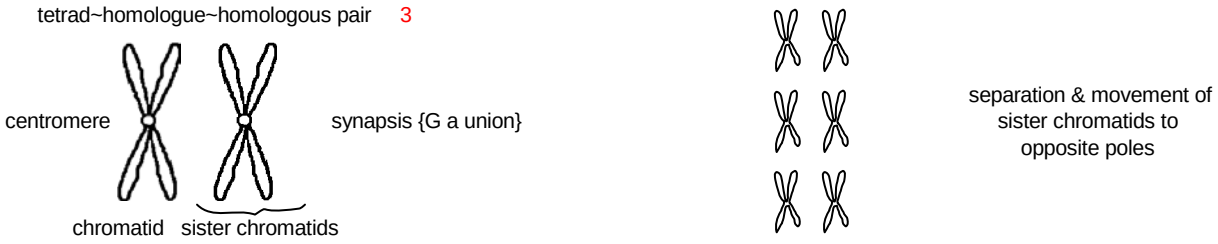


Figure IIIB-5. Terminology Relevant to the Tetrad (in Meiosis) TP IIIB-3

In meiosis, sister chromatids are formed (DNA strands are replicated) & then homologous pairs undergo synapsis [line up side by side]. Then one member of one pair goes to one pole & the other member goes to the opposite pole in a process called disjunction.

B.b.C. PATTERNS OF INHERITANCE (Mendelian Inheritance)

Term	Genotype	Phenotype {G appearance}
1) Homo\zygous {G same\G pair}	AA or aa	
2) Hetero\zygous {G different\}	Aa	
1) Dominant	AA or Aa	A
2) Incomplete Dominance	Aa	Aa
3) Codominance	Aa	A & a
3) Recessive	aa	a

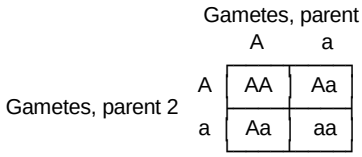


Figure IIIB-6. Terms Relevant to the Descriptions of Alleles & the Punnett Square TP IIIB-4

B.c. GENETIC & ENVIRONMENTAL DISORDERS

1) Hereditary source alone, 80%; environmental source w/ hereditary source, 20%

2) US incidence: 250,000/yr w physical or mental damage; 60,000 deaths due to birth defects//yr

B.c.A. GENETIC DISORDERS

B.C.A.a. SINGLE GENE DISORDERS

1) Each of us carries 5-8 genes (out of 30,000) w/ a recessive allele for a genetic disorder; 4-6 are inherited, 1-2 are mutations
2) 4000 single-gene disorders, e.g.:
   autosomal dominant: Marfan's syndrome
   autosomal recessive: cystic fibrosis, PKU, sickle-cell disease
   x-linked~sex-linked recessive: color blindness, hemophilia A, Duchenne muscular dystrophy
3) 1% of all adult admissions are due to single gene disorders

B.c.A.a.(A.) DISORDERS OF AUTOSOMAL INHERITANCE

B.c.A.a.(A.a.) DISORDERS INVOLVING AUTOSOMAL DOMINANT GENES

1) Mutant gene → defective structural or regulatory consequences
2) Later age of onset
3) Reduced penetrance: (20% penetrance = if have it, it will be expressed 20% of time –> skipped generations.)
4) Variable expressivity: 1 genotype –> several phenotypes TP IIIB-4a

B.c.A.a.(A.b.) DISORDERS INVOLVING AUTOSOMAL RECESSIVE GENES

1) Mutant gene –> defective enzyme
2) Early age of onset
3) ?Complete penetrance
4) Uniform expressivity

B.c.A.a.(A.c.) DISORDERS INVOLVING LETHAL AUTOSOMAL RECESSIVE GENES

As implied, aa is a lethal form, usually *in utero*. Aa is usually sublethal. (e.g. retinoblastoma P IIIC-2)

B.c.A.a.(B.) DISORDERS OF X-LINKED~SEX-LINKED INHERITANCE

1) X-linked [on the part of the X-chromosome not found on the Y-chromosome], therefore usually recessive:

genotype: phenotype:

Gametes, parent 1

Gametes, parent 2	X	x (defective allele)	
X	XX	Xx	♀X ♀X
Y	XY	xY	♂X ♂x

Figure IIIB-7. Punnett Square for Sex-linked Characteristics TP IIIB-5

B.c.A.a.(C.) MANIFESTATIONS OF SINGLE GENE DISORDERS
B.c.A.a.(C.a.) STRUCTURAL PROTEIN DEFECTS

1) Usually autosomal dominant
2) Because structural proteins are so widespread (e.g. connective tissue proteins), effects are often systemic w abnormalities showing up in several places.

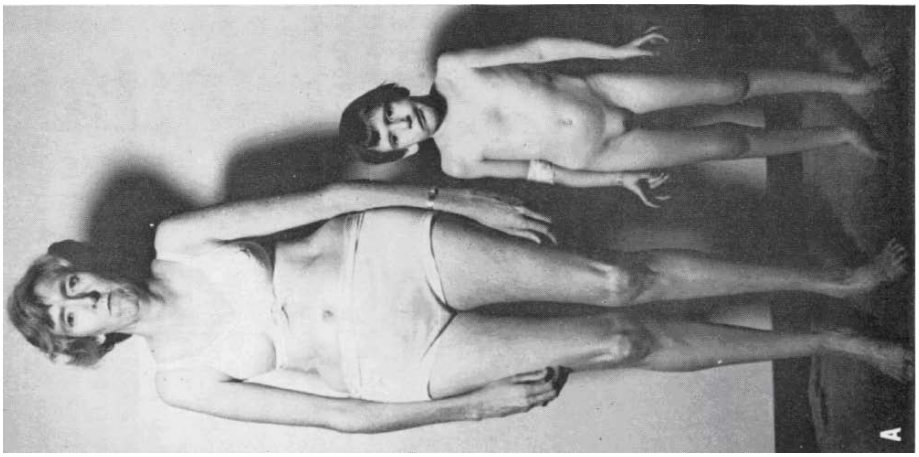


Figure IIIB-8. Mother & Daughter w/ Marfan Syndrome (6, p 168) TP IIIB-6

B.c.A.a.(C.b.) PRIMARY ENZYME DEFECTS

1) Usually autosomal recessive
2) Mechanisms:
   a) Deficiency at some pt in metabolic pathway → deficiency of end product

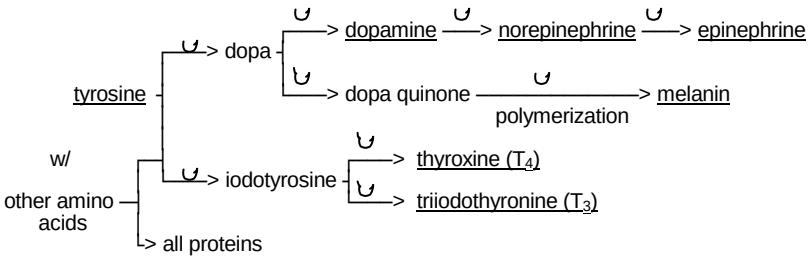
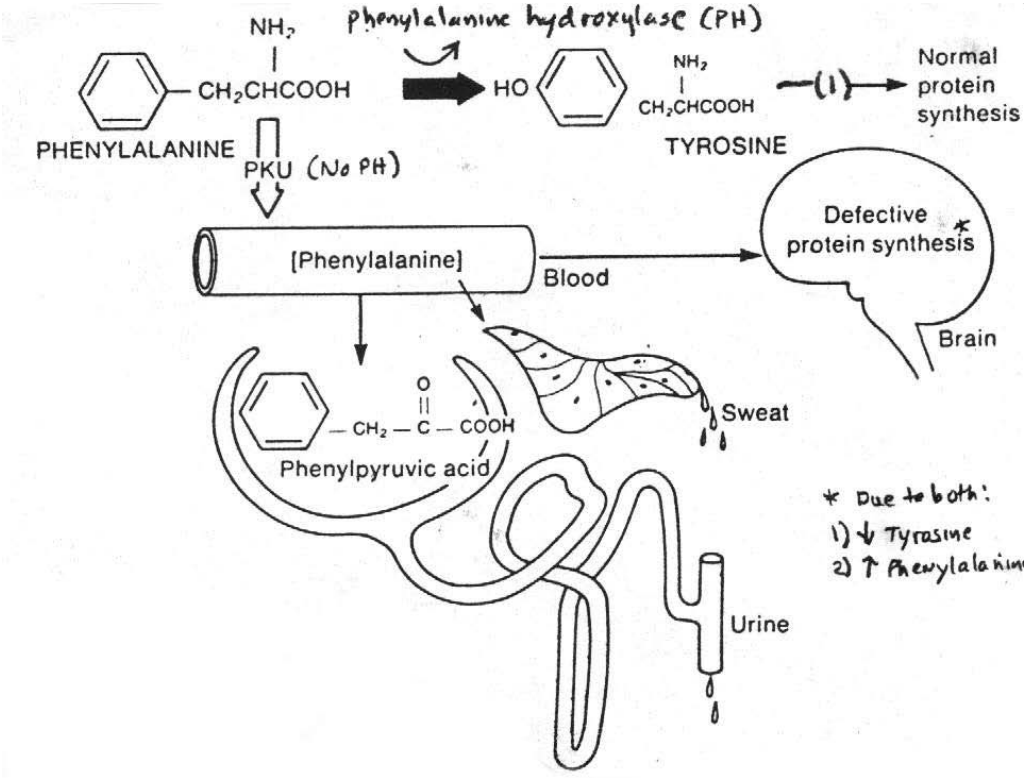


Figure IIIB-9. Products Involving Tyrosine Metabolism (7, pp 1221 & 1480) TP IIIB-7

   b) Production of harmful intermediates or toxic by-products of metabolism
   c) Accumulation of destructive substances due to ineffective enzyme (Fig IIIB-10)



KEY: 1: F IIIB-9: tyrosine essential to all proteins

Figure IIIB-10. Development of Phenylketonuria in the Absence of Phenylalanine Hydroxylase (5, p 33) TP IIIB-7

B.c.A.b. POLYGENIC DISORDERS

Several genes (# unknown) + proper environmental factors → high expressivity

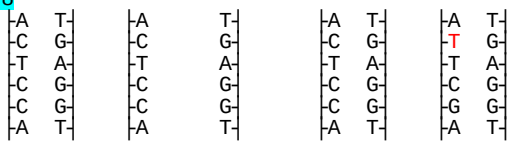
Include 1) congenital defects
cleft lip or palate, club foot, congenital heart disease, an\encephaly {G brain - no cerebrum}
2) post-partum defects
allergies, diabetes mellitus, essential hypertension

B.c.A.c. CHROMOSOME DISORDERS

Problems occur during duplication, synapsis & anaphase (PMAT)

B.c.A.c.(A.) ALTERATIONS OCCURRING DURING CHROMOSOME DUPLICATION (Replication)

TP IIIB-8



mutation –> defective m-RNA –> wrong aa –> defective 1° structure –> defective 3° structure –> defective function

Figure IIIB-11. How an Error in Replication can Lead to a Mutation

1) uncorrected mutation in meiosis (i.e. parent did not have mutation) –> death of offspring, through congenital defect, to no effect at all
2) uncorrected mutation during mitosis –> two lines of cells (mosaicism) – vitiligo (loss of melanocytes) port wine stain

B.c.A.c.(B.) ALTERATIONS OCCURRING DURING SYNAPSIS AND DISJUNCTION (alterations in chromosome structure)

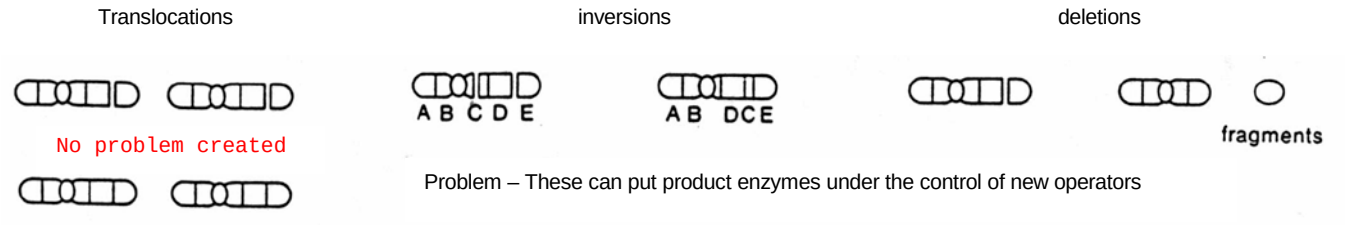
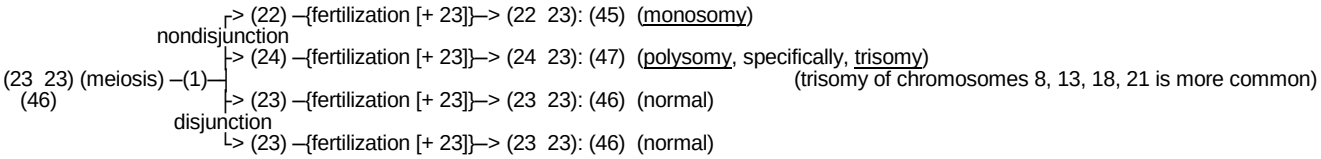


Figure IIIB-12. The Three Major Types of Changes in Chromosome Structure (32, p 63) TP IIIB-9

B.c.A.c.(C.) ALTERATIONS IN CHROMOSOME NUMBER (Aneu\ploidy) {G without\}
B.c.A.c.(C.a.) NONDISJUNCTION [homologous pairs or sister chromatids don't go to opposite poles, they go to the same pole]



KEY: 1: F IIIB-5: arrangement of chromosomes in synapsis

Figure IIIB-13. Nondisjunction, Monosomy & Trisomy TP IIIB-10

B.c.A.c.(C.b.) EXAMPLES

1) trisomy 21 –> Down's Syndrome; 2N = 47, up to 3 copies of genes in trisomy 21 –> too many enzyme products –??–> Down's

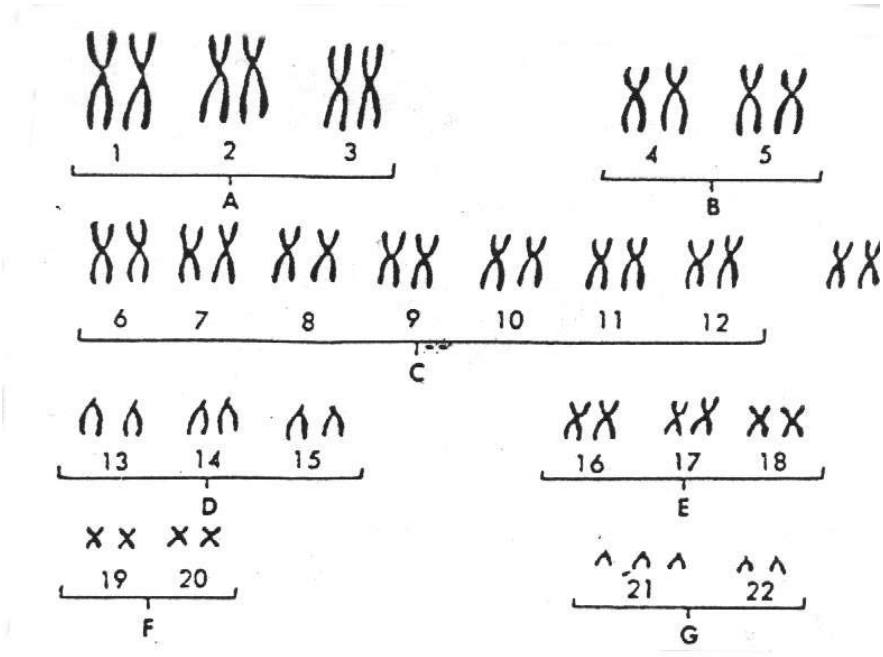


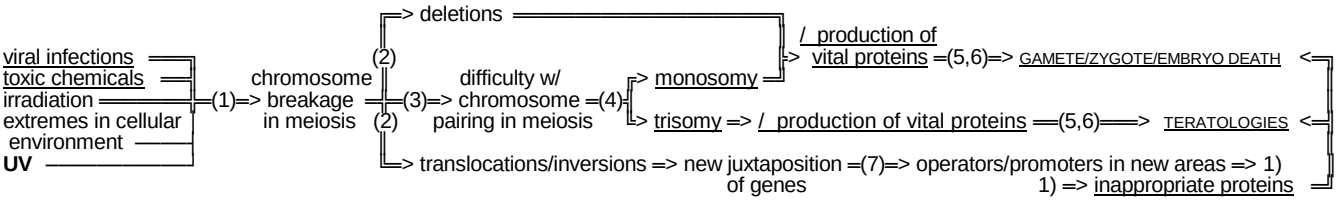
Figure IIIB-14. Karyotype of Trisomy 21 (5, p 37) TP IIIB-10

2) monosomy X –> Turner's Syndrome 2N = 45 [44,X\0) (no second X) male or female? 1//2500 live births, gonadal agenesis

3) polysomy X –> Klinefelter's Syndrome 2N = 47 [44,XXY] –> testicular dysgenesis [small, dysfunctional testes]

B.c.A.a.(D.) PATHOPHYSIOLOGY

ef's: viral infections, toxic chemicals, ionizing radiation, extremes in cellular environment, & UV
Syndrome: DEATH OF GAMETE, ZYGOTE, EMBRYO, FETUS or TERATOLOGIES



Key: 1: S III.A.b: mechanisms of cell injury
2: S III.B.c.A.c.(B.): alterations during synapsis
3: S III.B.c.A.c.(C.): alterations in chromosome numbers
4: F IIIB-13: nondisjunction
5: P IIIB-2: roles of proteins in developmental pathways
6: F IIIB-15: susceptible periods for birth defects
7: F IIIB-1, IIIB-2: control of protein synthesis

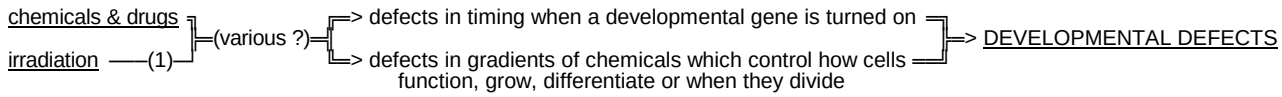
Path IIIB-1. Pathophysiology of Alterations in Chromosome Structure HWA

B.c.B. ENVIRONMENTAL DISORDERS

B.c.B.a. MUTAGENIC AGENTS [ef's → mutations]

B.c.B.b. TERATOGENIC AGENTS [ef's → teratologies] (birth defects)

ef's: chemicals, drugs, & irradiation~ionizing radiation



Path IIIB-2. General Etiology of Teratogenic Agents KEY: 1: CP IIIA-11: pathophysiology of ionizing radiation HWA

B.c.B.b.(A.) PERIOD OF VULNERABILITY

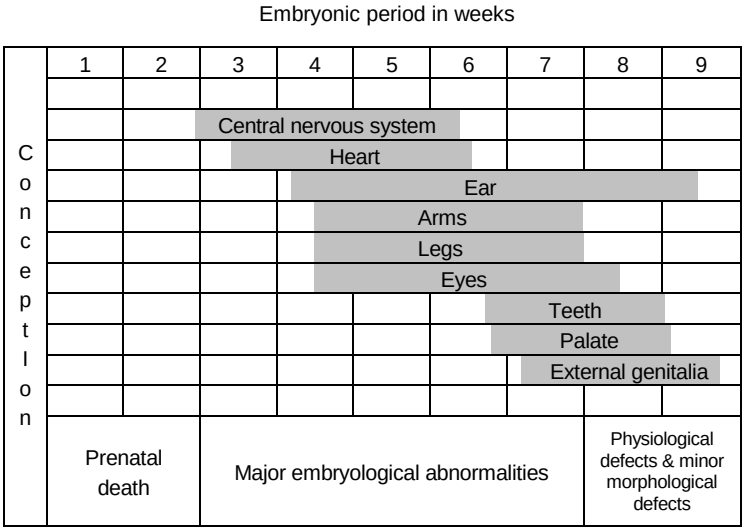


Figure IIIB-15. Susceptible Periods During Embryonic Development when Teratogenic Agents Have Profound Effects (32, p 64) TP IIIB-11

B.c.B.c. CARCINOGENIC AGENTS [ef's that cause cancer] (S III.C)

B.c.B.d. INFECTIOUS AGENTS [ef's that cause genetic changes] (S III.C & S IV.B)