REVIEW

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ENVIRONMENTAL MUTAGENS

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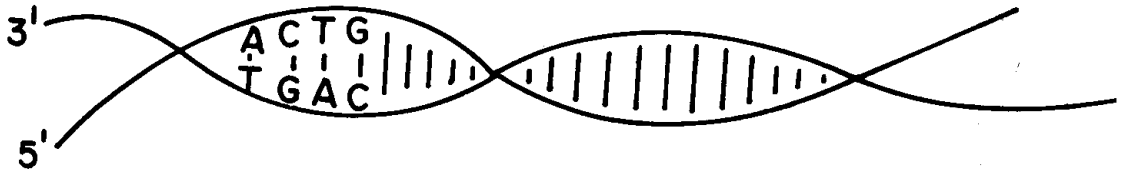
There is a unifying aspect in the storage, expression and transmission of the information that defines the spatial and temporal patterns of life, from the simplest virus to man. This information is programmed from a linear sequence of only two purines and two pyrimidines linked by sugar and phosphate bridges to form deoxyribonucleic acid (DNA), the genetic material common to all organisms (Figure 1).



A = Adenine
C = Cytosine
G = Guanine
T = Thymine

Figure 1. The double helical structure of DNA

The central dogma which is accepted as the basis of our understanding of how DNA functions is that the coded **messages** in this macromolecule are transcribed into messenger RNA (**ribonucleic acid) which then are**

translated into primary structure of proteins (Figure 2). The functions of these proteins can be catalytic, protective, regulatory, transport, and structu al.

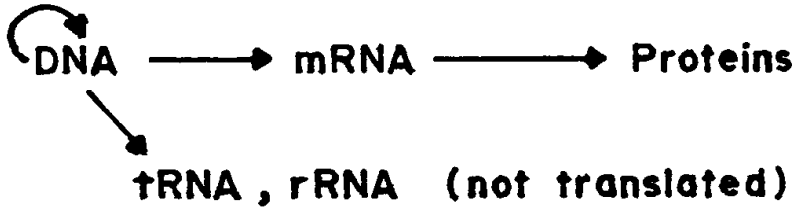


Figure 2. The central dogma: DNA-coded messages are transcribed into m-RNA and translated into proteins

There are, however, triplet codes of DNA which do not follow this precept. For example, there is a class of DNA in which the triplet code is only transcribed but is never translated in the case of DNA triplets that code for transfer RNA and ribosomal RNA.

Sections of DNA that code for proteins are known as exons (Figure 3a). The intervening sequences which do not code for proteins are called introns. The exons have unique nucleotide sequences. When transcribed into mRNA and then translated, these specify sequences of amino acids in proteins (Figure 3b).

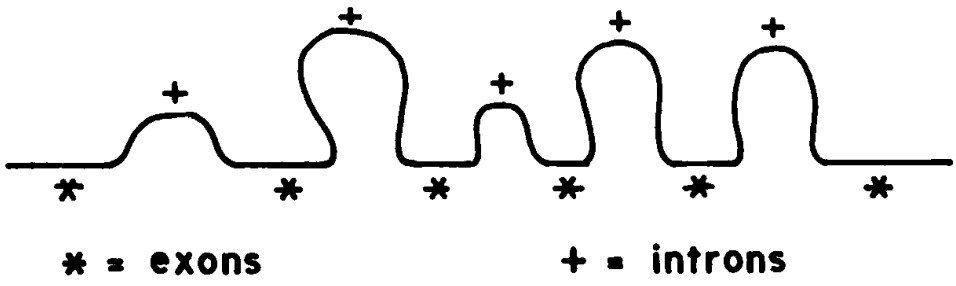


Figure 3a. A schematic diagram of exons and introns

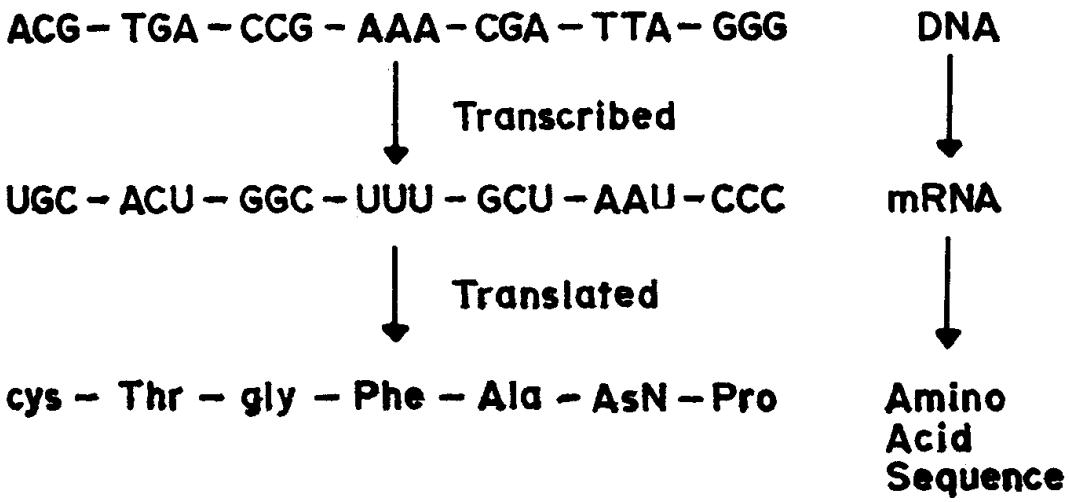


Figure 3b. How exons specify amino acid sequences

Any change in the electronic structure or in the base sequence of the exons, i.e., the genes coding for proteins, may lead to the production of non-functional proteins which may in turn lead to different phenotypic effects (1).

Changes in the structure of DNA can be induced by environmental mutagens which are of three basic types: physical (heat, ionizing and ultraviolet radiation, chemical, and viral. These may enter the human body through inhalation, ingestion, and skin penetration.

Physical Mutagens

Ionizing radiation such as X-rays and gamma rays can knock off electrons from target bonds. This can induce single and double strand breaks in the phosphodiester backbone of the duplex. If not repaired, various bonds may be broken. With sparsely ionizing radiation such as X-rays, the ratio of single strand to double strand breaks is around 10 to 1, but with densely ionizing radiation (such as alpha particles or protons from fast neutrons) the majority of the breaks are double stranded (2). With X-rays, a single energy loss event of ~60eV produces a single-strand

break. Two such independently induced single strand breaks, if less than five bases apart, can result in a complete scission across both polynucleotide strands (Figure 4).

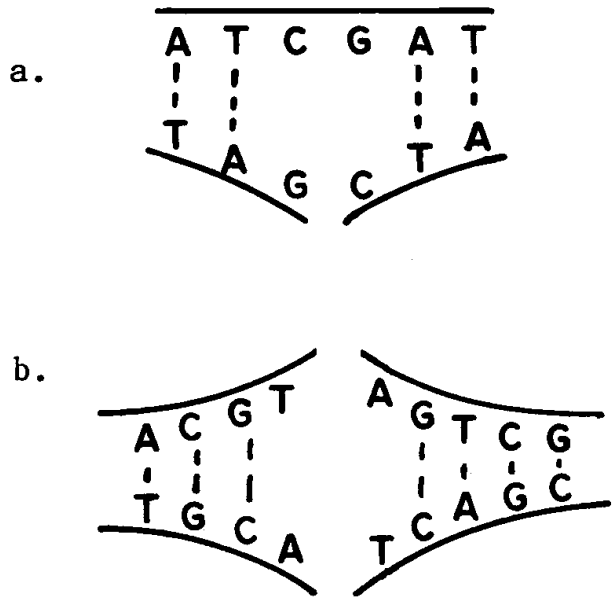


Figure 4. a) Single-Strand breaks; and b) double-strand breaks caused by ionizing radiation.

On the cellular level, ionizing radiation may also knock off electrons from water molecules in the cytoplasm, leading to the formation of hydroxyl free radicals which can initiate free radical formation among the RNA bases, particularly thymine. This base can readily form free radicals and can induce the formation of other free radicals as illustrated in Figure 5 (3).

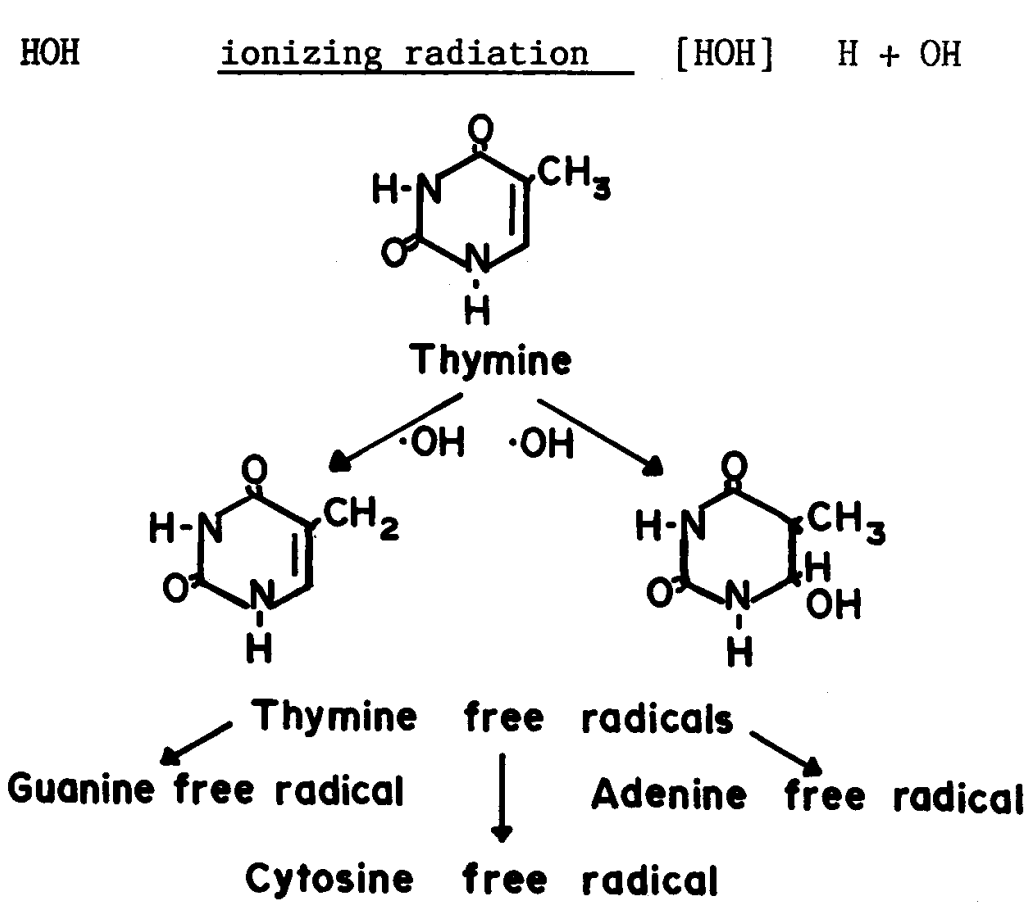


Figure 5. Free radical formation

Coupling of free radicals across strands may lead to rigid loops which may inhibit opening up of helices for replication and transcription (Figure 6).

Figure 6. Rigid loop formation

Addition of hydroxyl free radicals across the 5,6-bond of thymine or cytosine may alter their electronic char-

acteristics so that mispairs result (Figure 7).

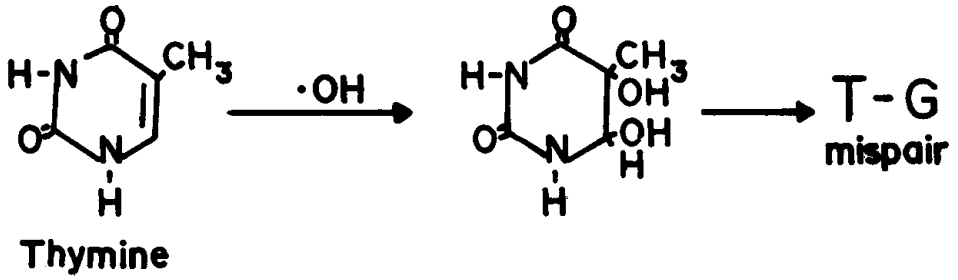


Figure 7. Mispairing as a result of free radical addition across the 5, 6-bond

Ultraviolet radiation causes the formation of thymine cyclobutane dimers in DNA, a consequence of the reactivity of the pi-electrons at the 5,6 position (4). The different conformational and electronic characteristics of these dimers give rise to abnormal interactions which result in faulty replication and transcription (Figure 8).

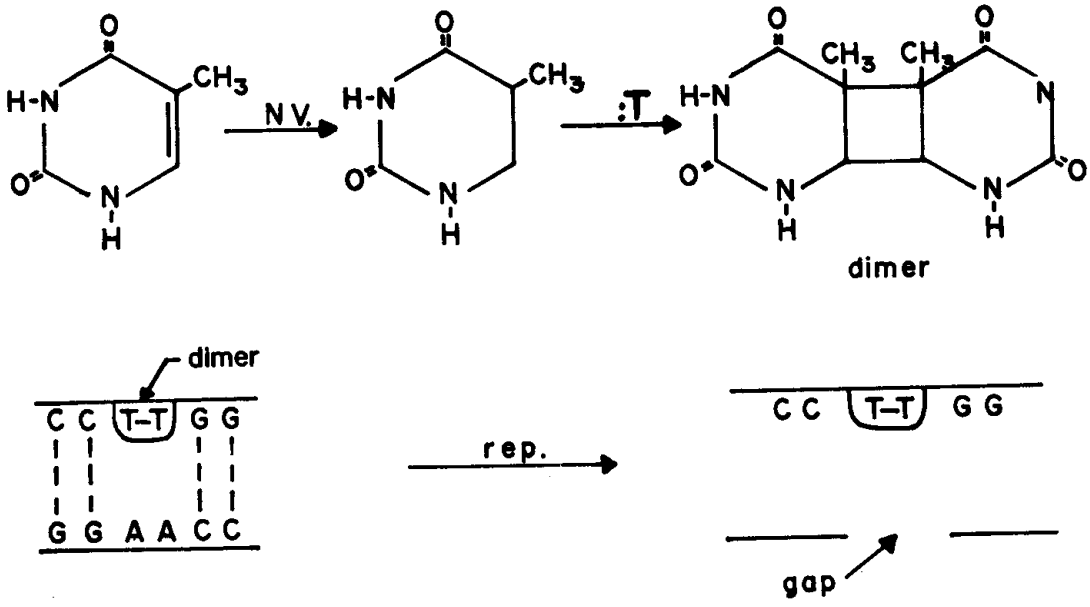


Figure 8. The effects of ultraviolet radiation

Heat can cause transmigration of the dipositive N-C glycosidic bond in guanine. This may lead to the formation of neoguanosine links (Figure 9) and ultimately to mispairs (5).

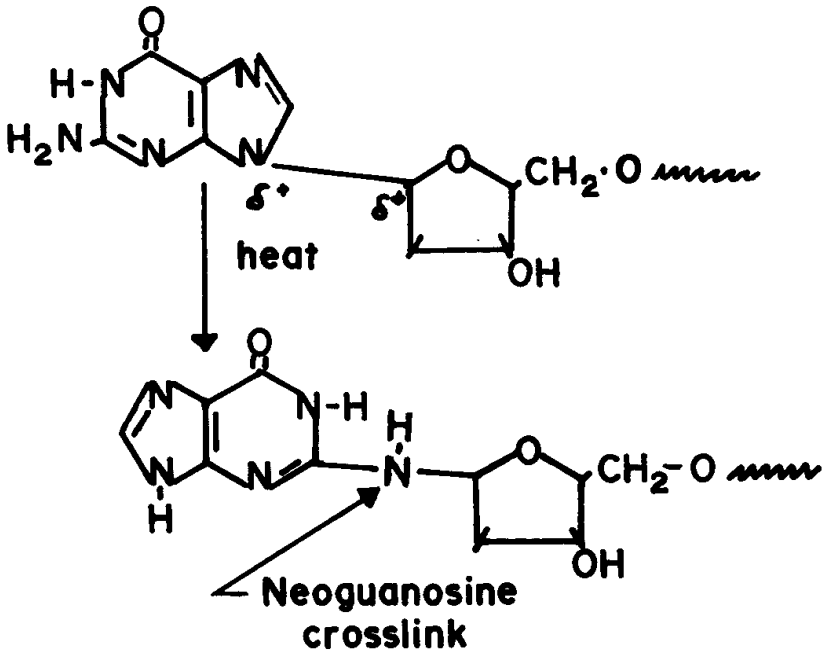


Figure 9. The effect of heat on guanine

Viral Systems

Mechanisms by which retroviruses transfer their genetic information from a single stranded RNA of their virions to a double stranded DNA linked to cellular chromosome have been proposed (6). One such mechanism is depicted in Figure 10.

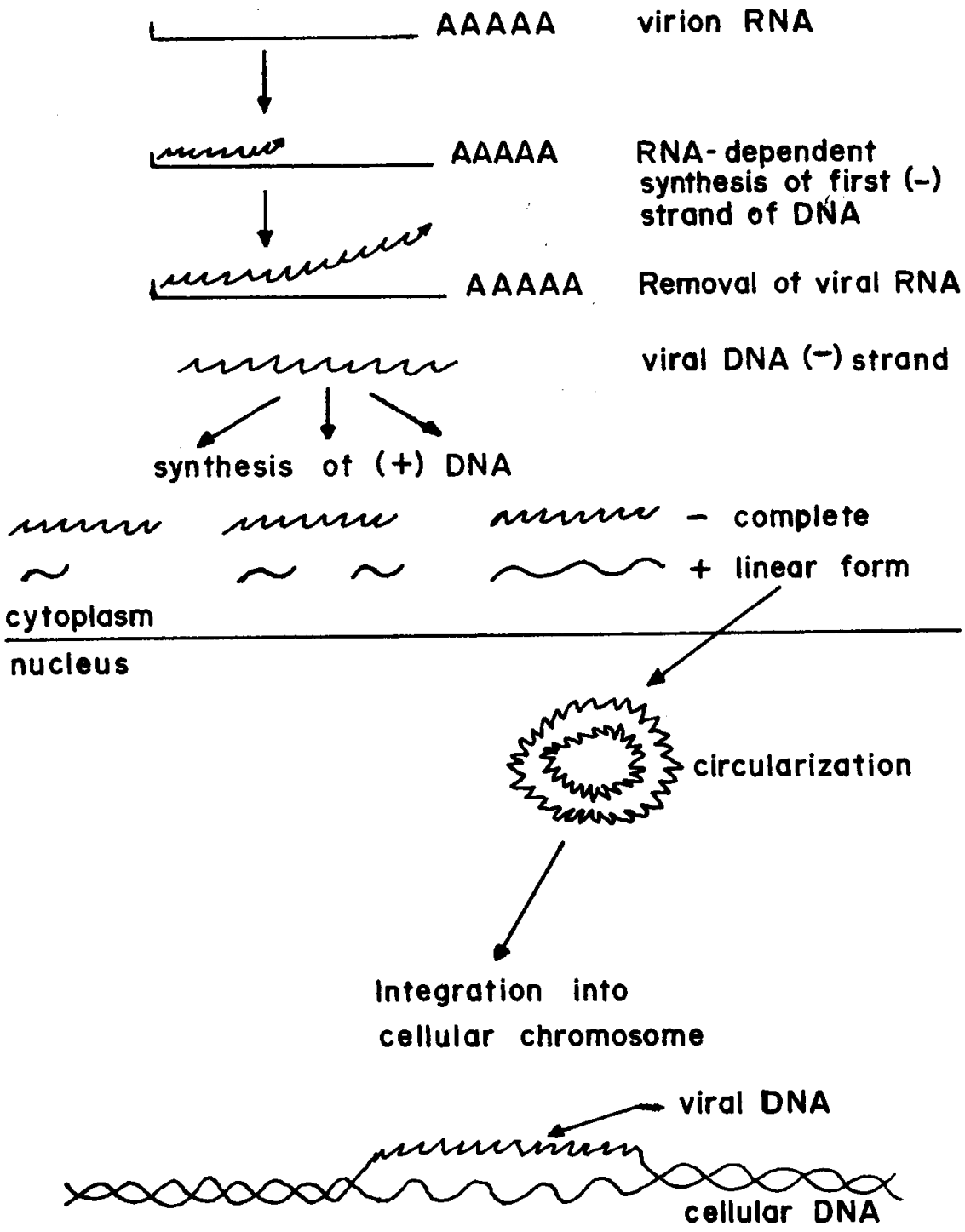


Figure 10. A mechanism whereby viral genetic information is incorporated into cellular DNA

It has also been proposed that the early steps of proviral synthesis occur in the nucleus, resulting in the covalent integration of viral RNA-DNA hybrids into cellular chromosomal DNA (7).

Chemical Mutagens

Chemical mutagens may be of natural or synthetic origin. A chemical mutagen after having reached the blood stream is carried to all organs and tissues within less than one minute. By passive or active absorption, the substance then penetrates the capillary lining and enters adjacent cells. Although significant barriers exist in some tissues such as the brain and the placenta, there are mutagens that can breach these barriers. A substance is called a direct mutagen if it interacts with DNA directly; if it interacts with DNA only after metabolic activation, it is called a pro-mutagen.

Some chemical systems with polycyclic planar structures can interact with DNA through intercalation causing the formation of extrahelical loops (Figure 1) (8).

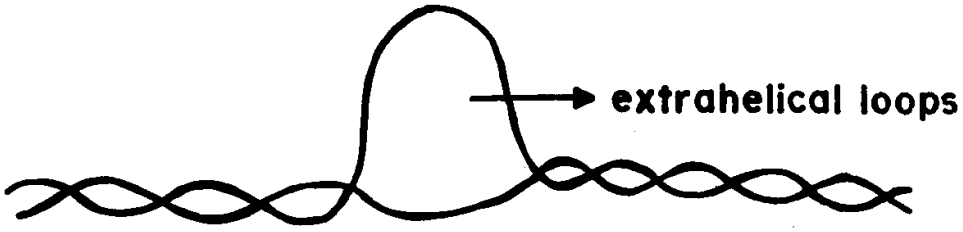
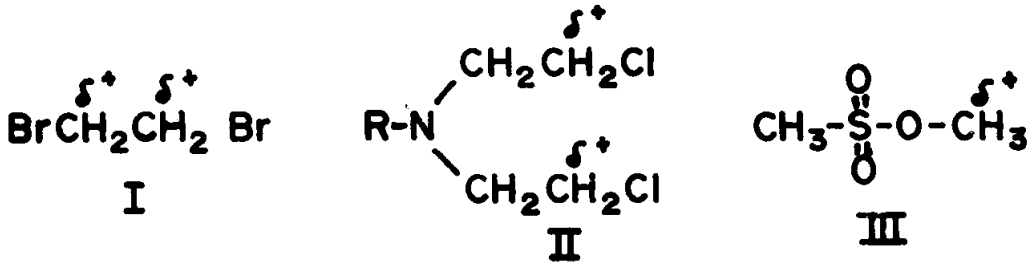


Figure 11. Extrahelical loops caused by interaction

Other chemicals alter DNA structure by alkylation reactions. These chemical agents either have electrophilic sites or are metabolized to electrophiles which

can readily interact with alkylation sites at DNA bases. Compounds I-III contain electrophilic sites.



δ+ = electrophilic sites

A number of alkylation sites have been proposed by Singer (9). These include all nitrogens of the bases, O^6 of guanine, and O^2 and O^4 of thymine, the N^7 of guanine being the major alkylation site and all others being minor although alkylation of guanine at O^6 has been observed to be more persistent than at N^7 (10). N^7-alkylation easily leads to apurinic sites which are readily repaired; alkylation at O^6 leads to well-fitting mispairs (Figure 12) (11).

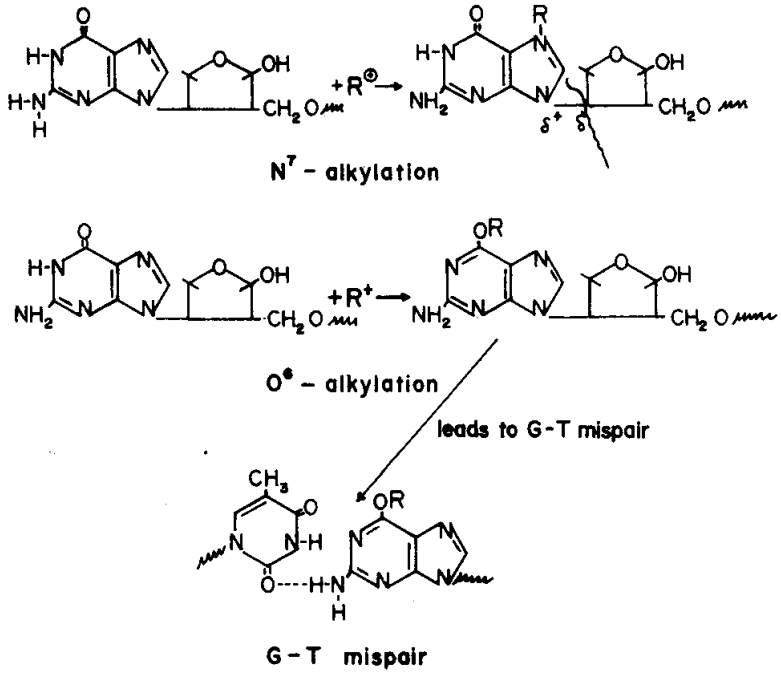


Figure 12. N^7- and O^6-alkylation

As mentioned earlier, a number of chemical mutagens become alkylating agents only after metabolic activation. Examples are N-nitrosoamines, polycyclic aromatic hydrocarbons, aflatoxins, and aromatic amines, which are very readily metabolized by liver enzymes.

A proposed metabolic pathway for N-nitrosoamines is shown in Figure 13 (12). In this mechanism, a carbocation is the active alkylating agent.

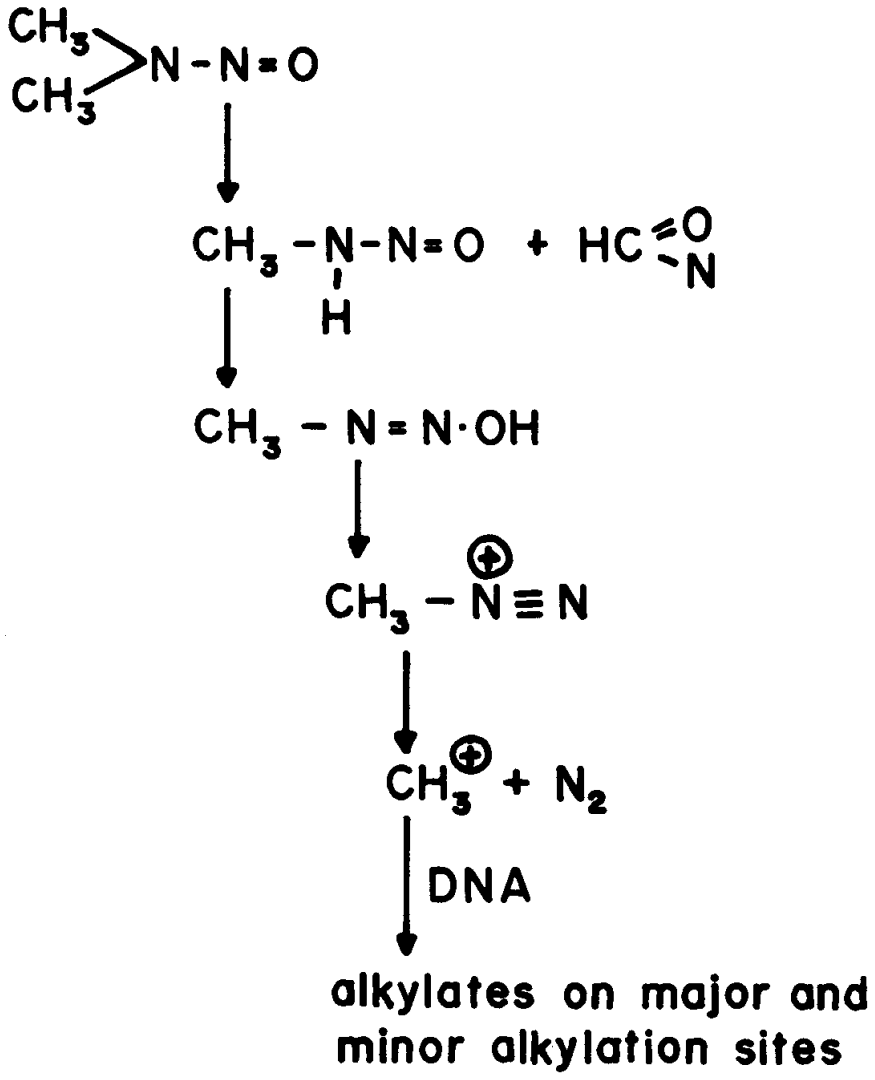
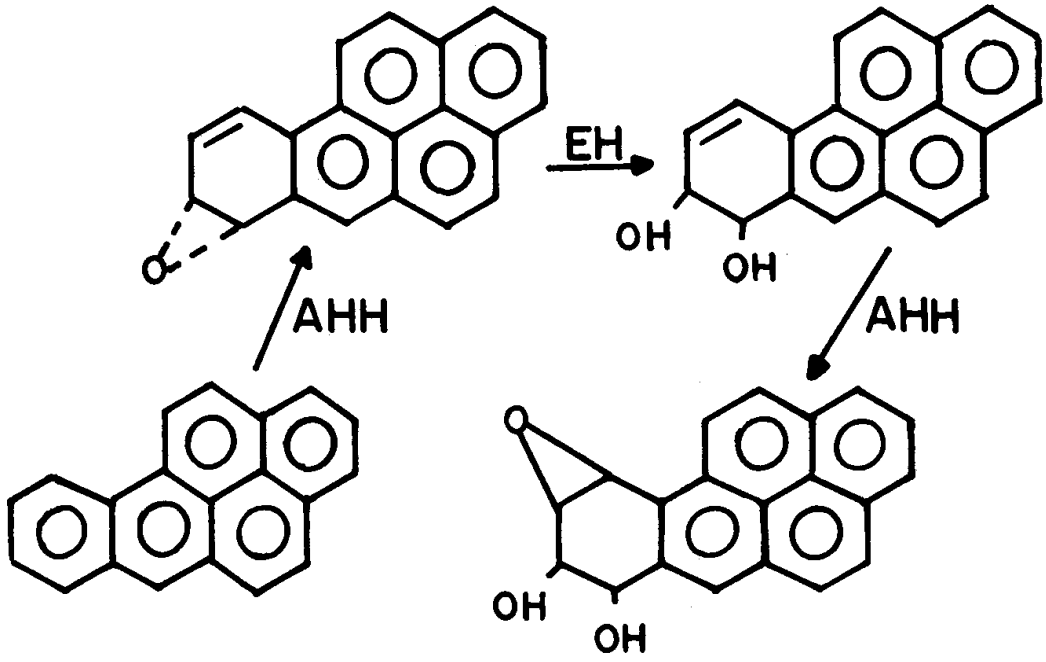


Figure 13. The metabolic pathway for N-nitrosamine

In the case of the polycyclic aromatic hydrocarbon benzopyrene, the formation of diolepoxides (Figure 14) has been proposed (13). Each type of diolepoxide can readily alkylate DNA. The metabolic pathway for a very potent diolepoxide has been proposed (14).



AHH – aryl hydrocarbon hydroxylase

EH – epoxide hydrase

Figure 14. The formation of diolepoxides

Aflatoxins B_1 and G_1 both have a pi bond at the 2,3-position. As a result these can be easily converted by liver enzymes into 2,3-epoxides which are very active alkylating agents, epoxide carbons being very electrophilic (Figure 15). Microsomal oxidation of aflatoxin B_1 to the 2,3 epoxide has been proposed by Swensen (15).

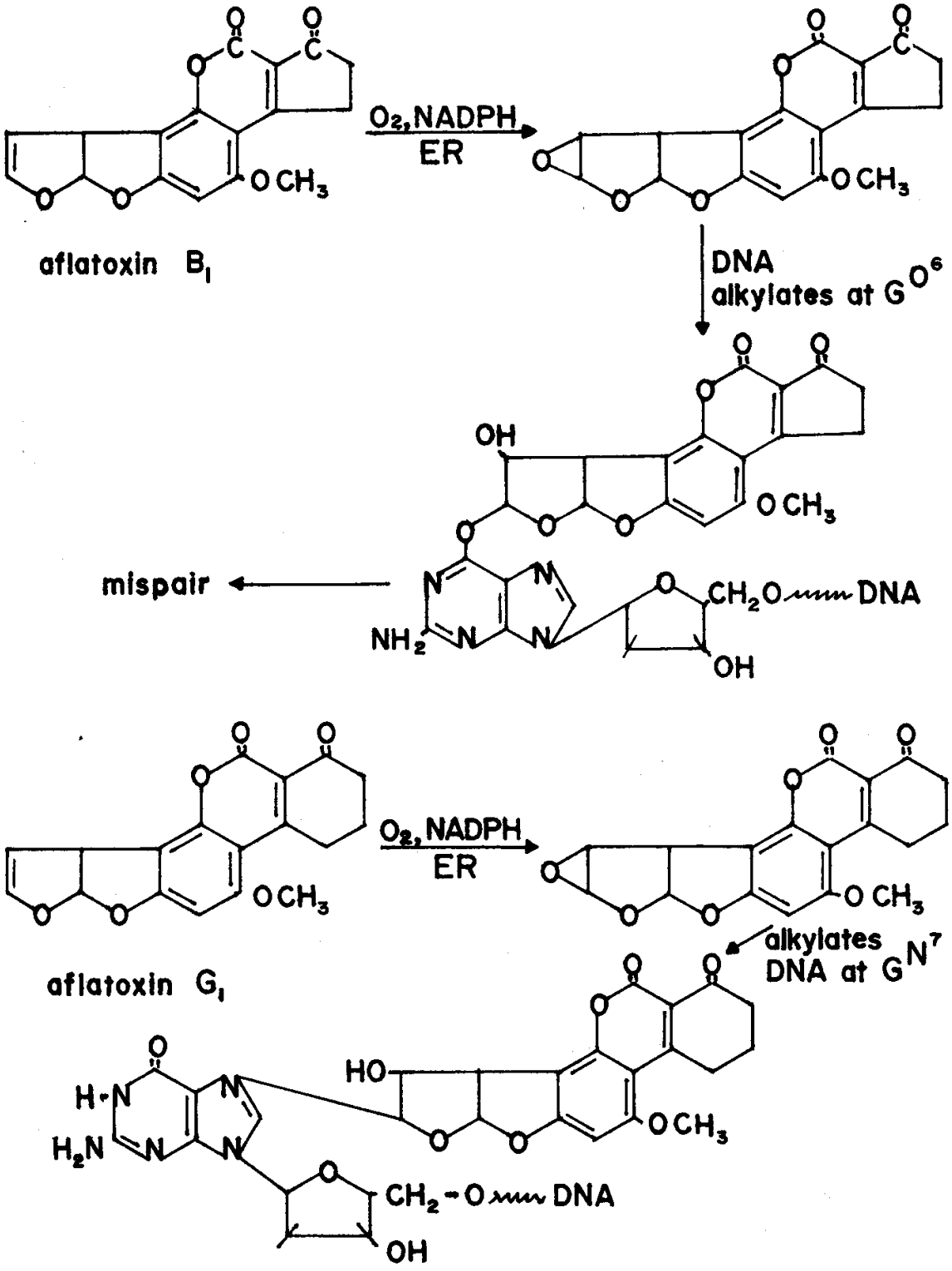


Figure 15. Epoxidation of Aflatoxins B_1 and G_1

N-hydroxylation is the important reaction in the metabolic breakdown of aromatic amines (16). The products of hydroxylation are converted by esterification to strong electrophiles (Figure 16).

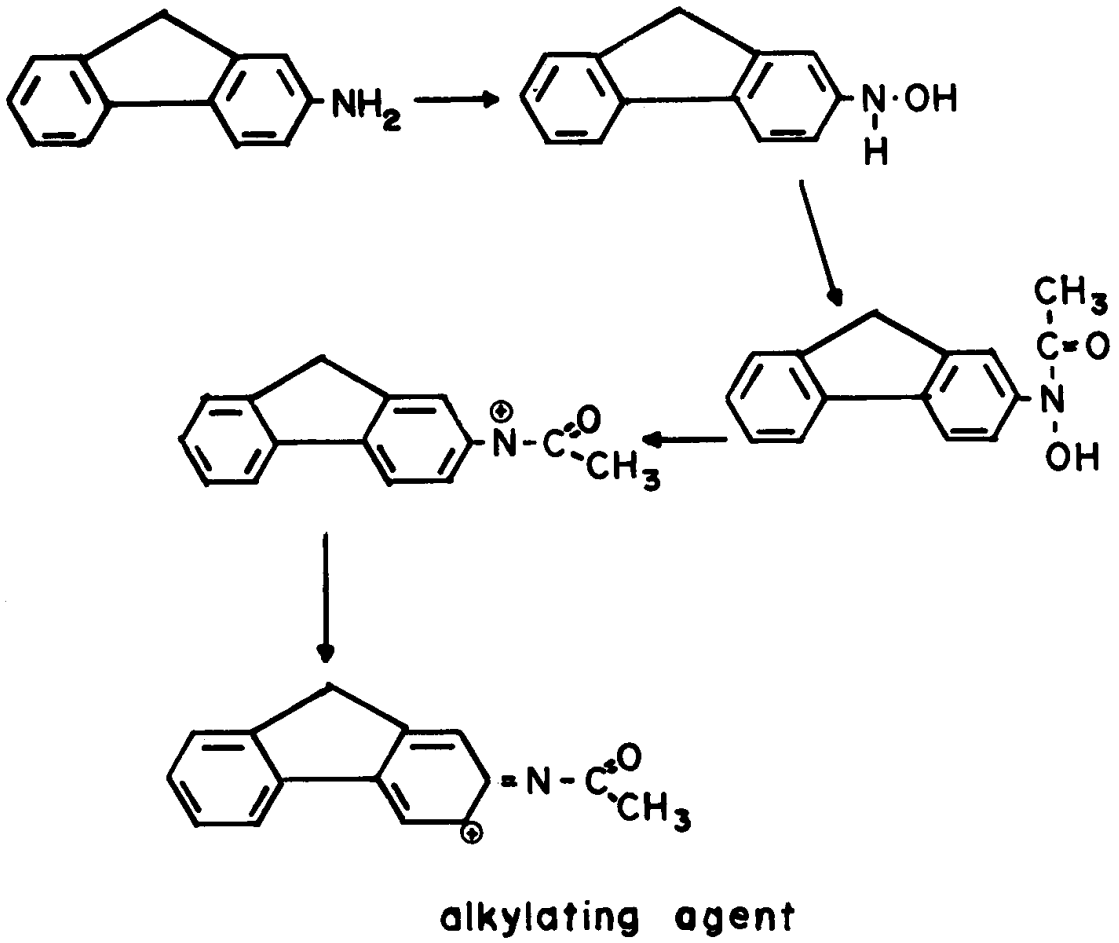


Figure 16. The metabolic pathway for aromatic amines

A number of industrial chemicals are also oxidized to compounds which can alkylate DNA. Vinyl chloride, chloroprene, styrene, and benzene are examples (17,18) . Their conversion to potent alkylating agents are illustrated in Figure 17.

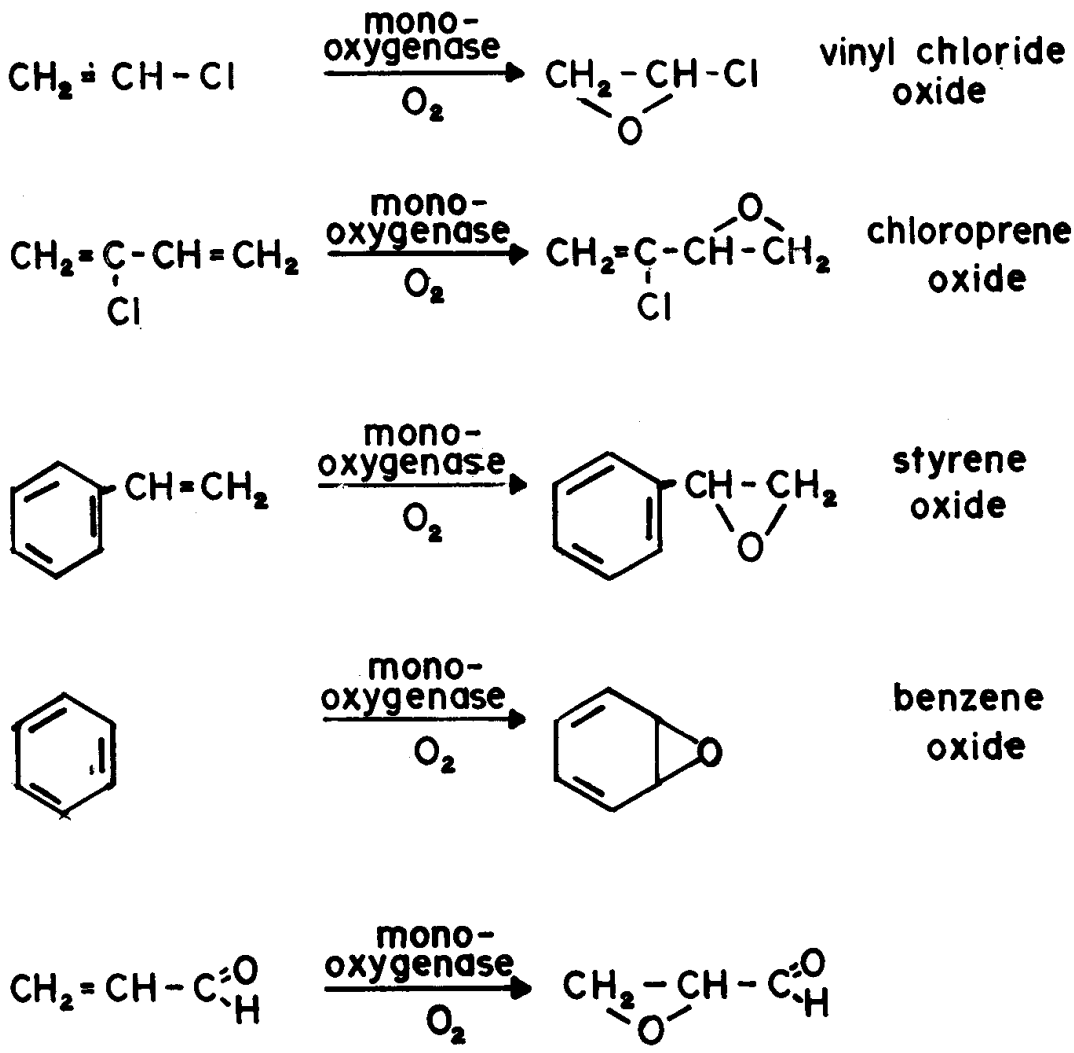


Figure 17. Enzymatic conversion of industrial chemicals to alkylating agents

Some chemical systems alter the structure of bases in DNA by addition to the 5-6 bond of pyrimidines. One such reaction is illustrated on Figure 18. Sulfur dioxide adds as bisulfite. Subsequent reactions result in the conversion of cytosine to uracil, ultimately leading to mispairs (19).

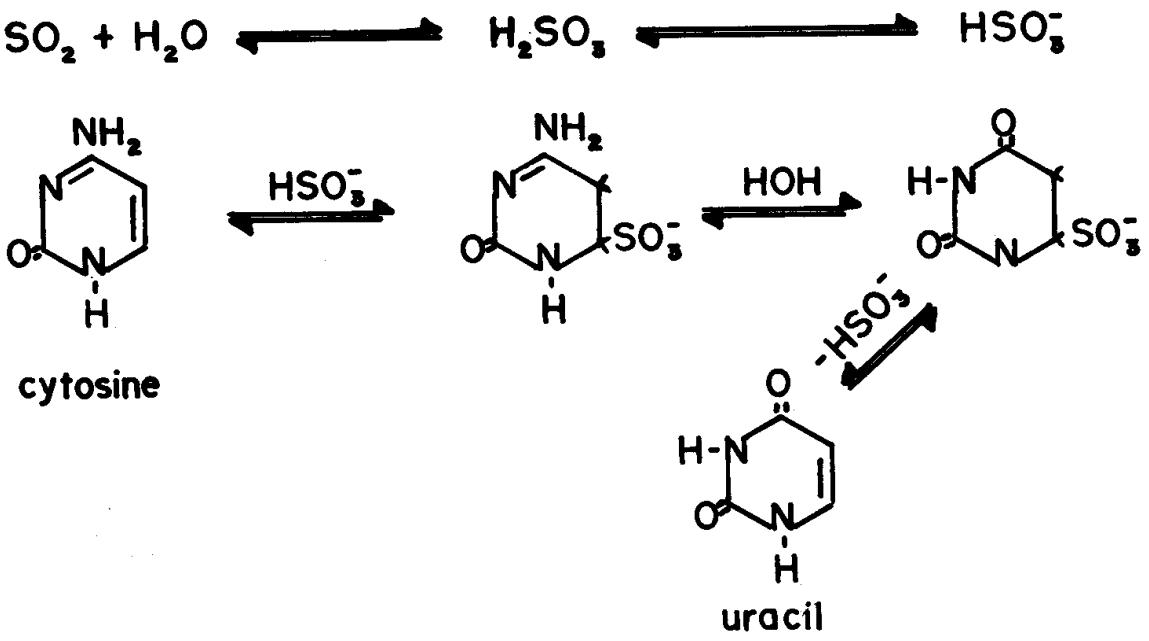


Figure 18. The reaction of sulfur dioxide with DNA

Some chemicals deaminate bases like adenine. This reactivity is illustrated by nitrous acid (Figure 19) (20). The conversion of adenine to hypoxanthine can cause mispairs.

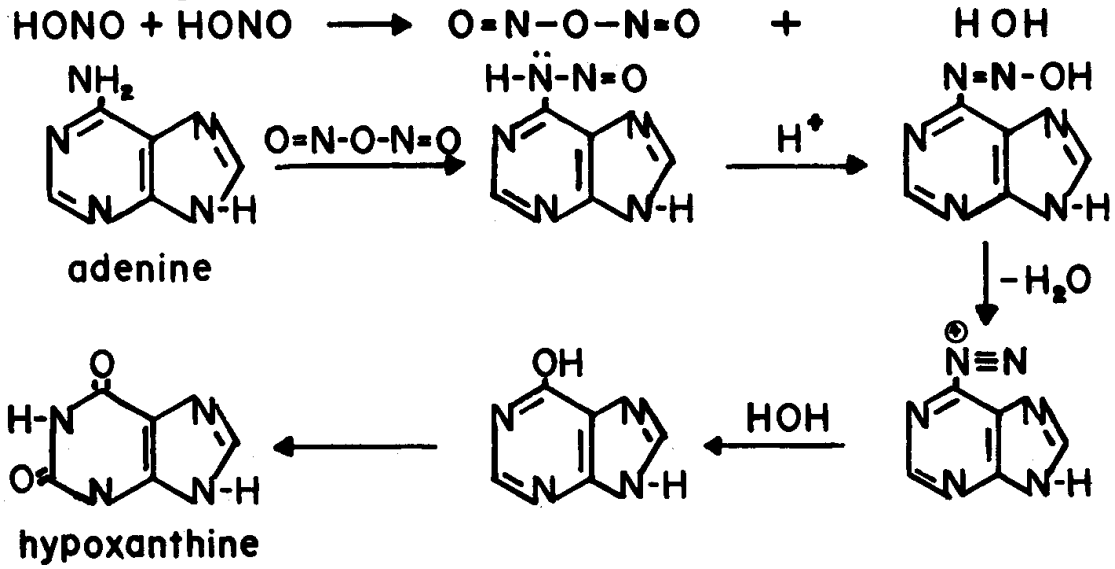
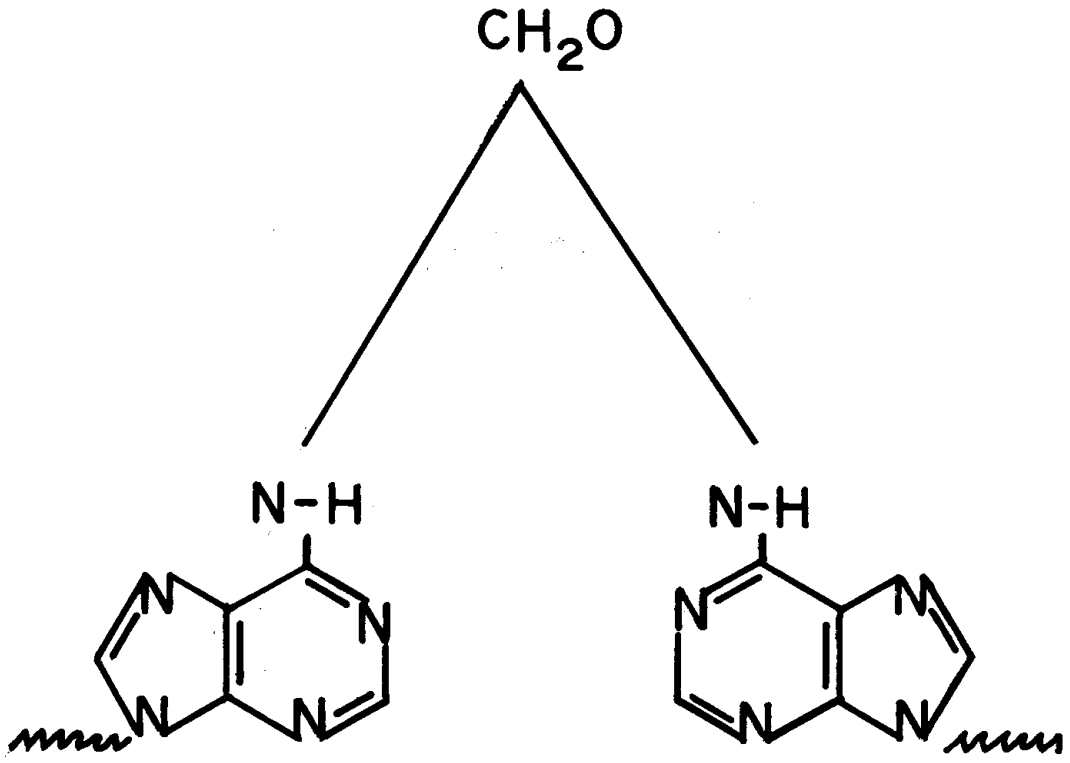


Figure 19. The reaction of nitrous acid with adenine

Formaldehyde also reacts with adenine resulting in the formation of bis adenosine IV (21).



IV

The mutagenic effects of lead, mercury, arsenic, and cadmium have been reported (22). Their mutagenicity can be a consequence of their tendency to interact with DNA polymerases (repair enzymes) so that the enzyme conformation becomes non-functional, possibly leading to misrepair. Interactions with methylmercury has been associated with the -SH, $-COO^-$ and $-NH_2$ groups of protein amino acids (Figure 20) (23).

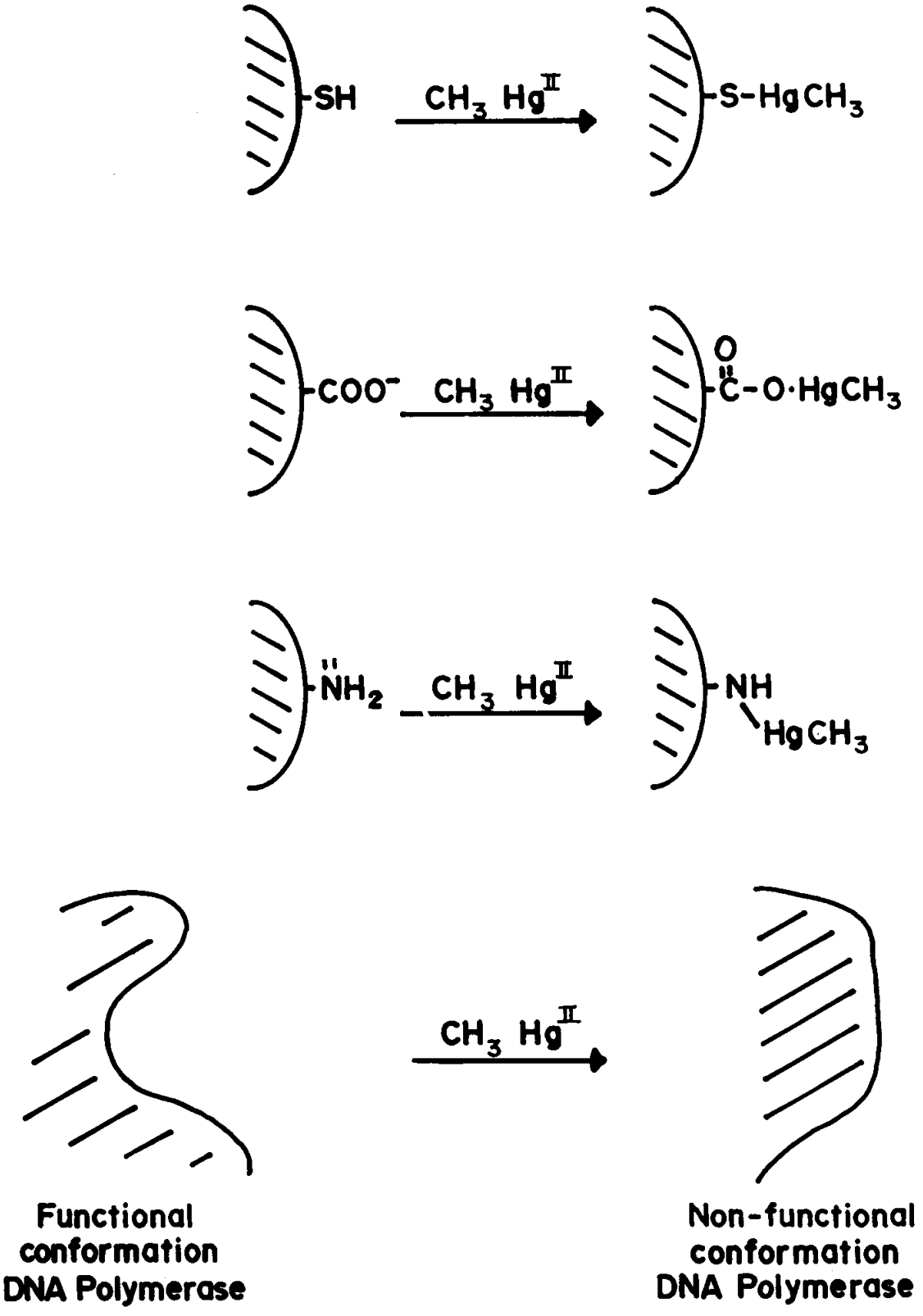


Figure 20. The interaction of methylmercury with protein amino acids

MUTATIONAL MECHANISMS

The effects of physical, viral and chemical mutagens can be categorized into the following mutational mechanisms (24):

1. Mispairs: Nucleoside modification can lead to direct mispairing, and thus can generate base pair substitutions which can either be transitions or transversions (Figure 21) (25). Deaminations, bisulfite additions, alkylations, and formation of rare tautomeric forms may lead to transitions. Mispairs that lead to transitions are usually well-fitting mispairs, i.e., those that can fit well into the groove of the helix such as the mispairing of cytosine with hypoxanthine brought about by the nitrosation of adenine.

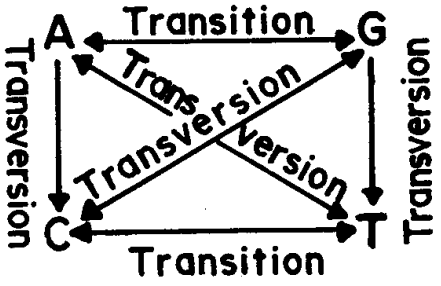


Figure 21. Mispairing as a result of transitions and transversions

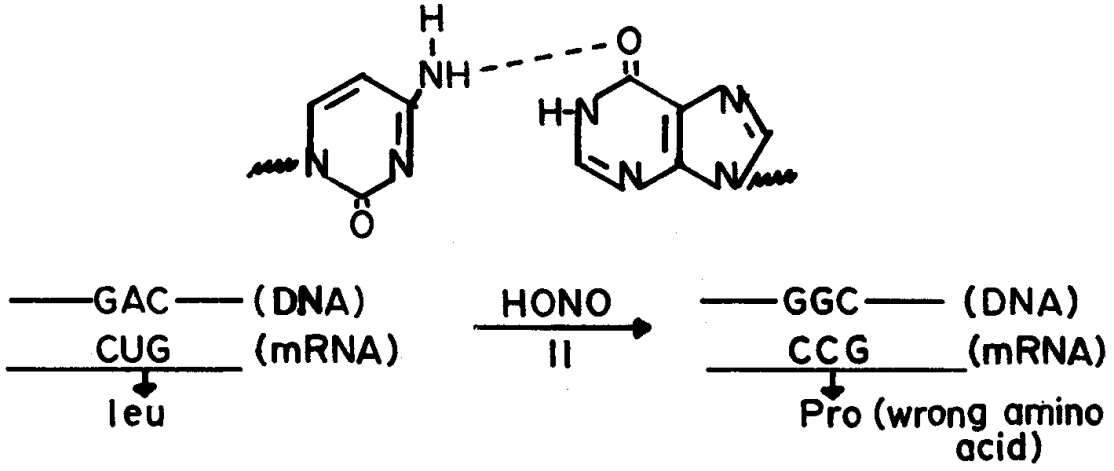


Figure 22. Error in amino acid coding as a result of base transactions

It is also impossible for transitions to lead to the incorporation of the wrong amino acid during protein synthesis. As illustrated in Figure 22, instead of coding for leucine, the altered DNA (A replaced by G) codes for proline.

In base transversion, a purine is substituted by a pyrimidine, i.e., replacement of G by T and of C by A. Heat, which leads to trans-migration of the N-C glycosidic bond in guanosine may induce transversions which may in turn also result in the coding of the wrong amino acid.

2. Frameshift mutagenesis: Misalignment of base sequences may lead to a change in the reading frame of the codes contained in DNA. These changes, called frameshift mutations, may arise from strand discontinuity. Intercalating agents, and the additions and deletions (Figure 23) of some bases may also induce frameshifts.

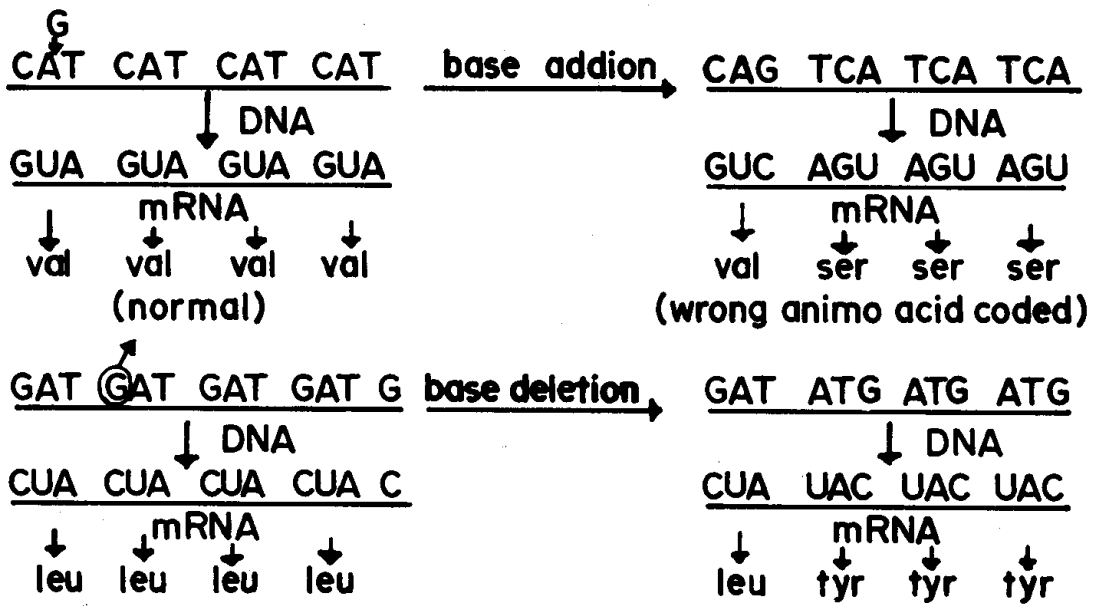


Figure 23. Frameshifts caused by base addition and deletion

3. Misrepair: Error-prone or mutagenic repair (Figure 24) is now known to be a major mutagenic pathway (26). A mutagen may induce changes in the amino acid sequence of a repair enzyme such as DNA polymerase, causing a loss of accuracy in copyediting or in recognizing the base sequence to be repaired. It is also possible for the mutagen to cause a change in the functional conformation of the repair enzyme. A repair enzyme may lose its precision in repairing gaps if modified bases are present that will not allow normal interactions with the enzyme.

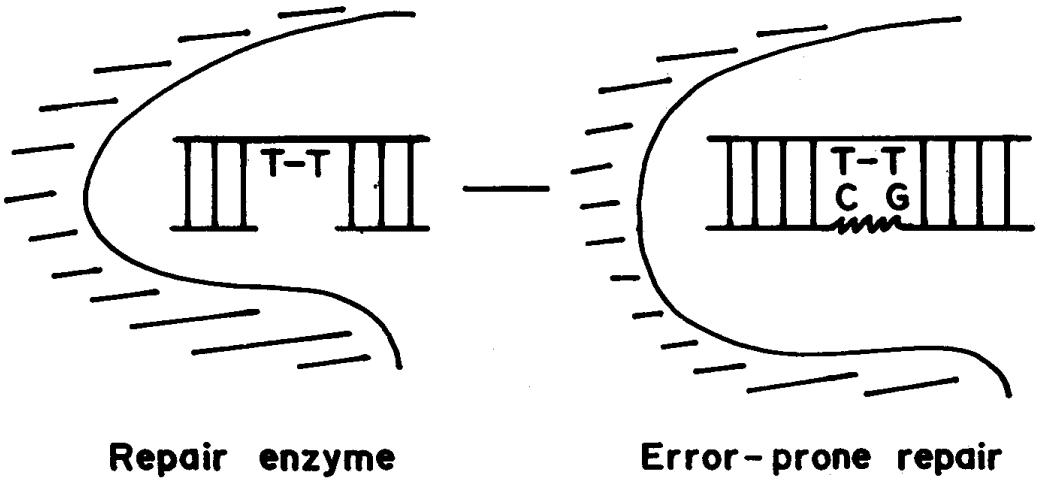


Figure 24. A mutagen may affect the action of repair enzymes

CAN DNA STRUCTURE BE READILY ALTERED?

At the nuclelosome level, DNA winds tightly around histones making it difficult for mutagens to reach the bases. However, there are some portions, or kinks, that are loosely bound where the bases become more accessible to mutagens (Figure 25).

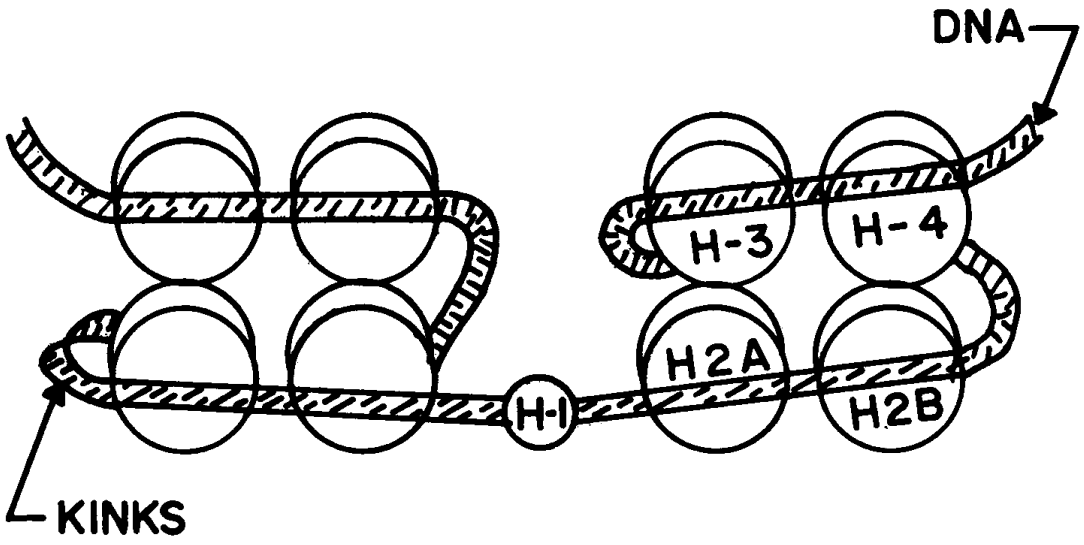


Figure 25. The nuclelosome structure of DNA

Although a number of interactions between base pairs would make it difficult for mutagens to react with the bases, there are stages in the cell cycle during which the double helix opens up for replication, transcription, and repair (Figure 26). It is during these stages when the bases can become more exposed for reaction with mutagens.

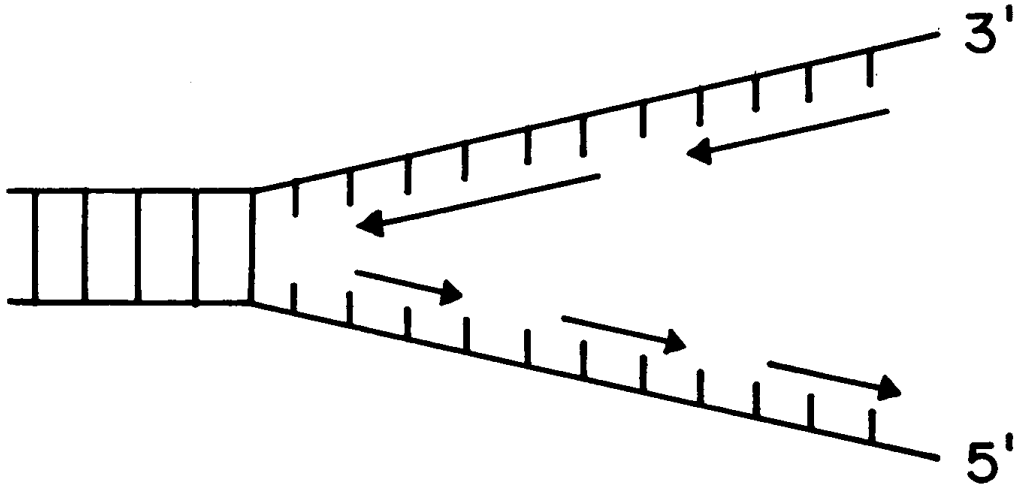


Figure 26. DNA replication

The DNA is, in the nucleus, protected by a nuclear membrane. The hydrophobic interior of the membrane would allow non-polar mutagens to penetrate it. Some polar mutagens can utilize a protein carrier to breach the barrier represented by the hydrophobic interior of the membrane.

The large percentage of repetitive sequences of DNA that do not code for any protein reduces the probability of a mutagen altering the code for a given protein and can account for the small number of nucleoside deletions when DNA, the structural gene material, is under the influence of mutagens.

WHAT ARE THE CONSEQUENCES OF MUTAGENIC REACTIONS?

The effects of some mutagens are reflected at the chromosomal level as illustrated in Figure 27.

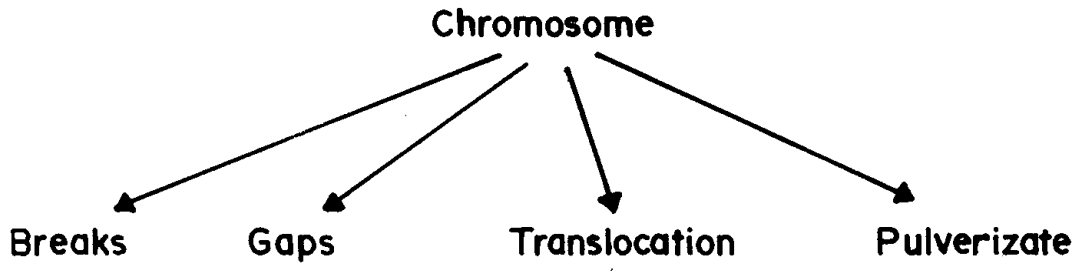


Figure 27. Mutagenic effects at the chromosomal level

After reacting with cellular DNA material, some mutagens may induce cell death. When cells die, there is usually no trace of the structural change. However, some structural changes are subtle enough to allow cells to survive as transformed somatic cells which, after a latent period of 20 years or so, may appear as cancer.

Changes in the DNA of germ cells may lead to sterility or genetic disorders that can be perpetrated from one generation to the next. All these changes are illus-

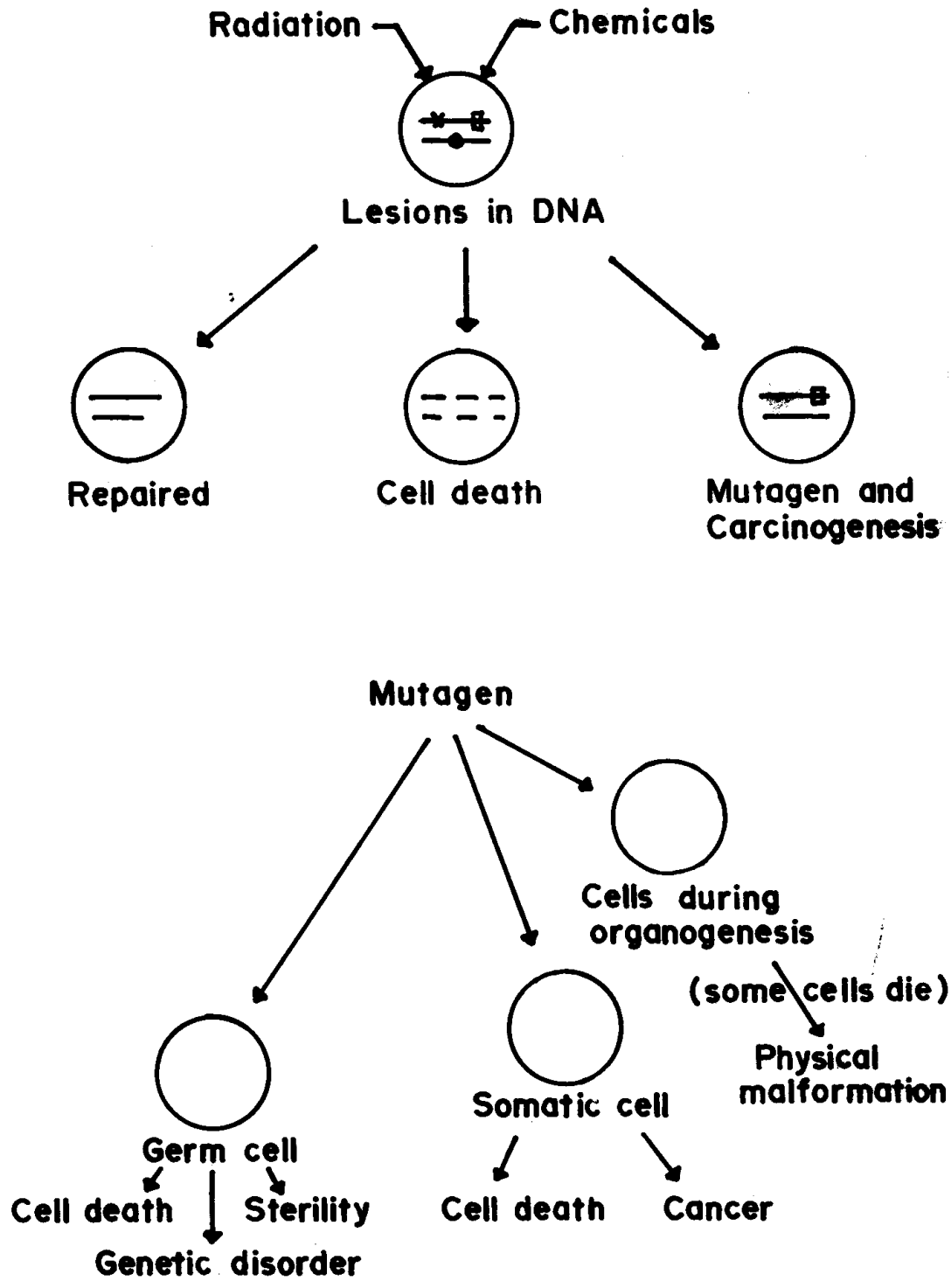
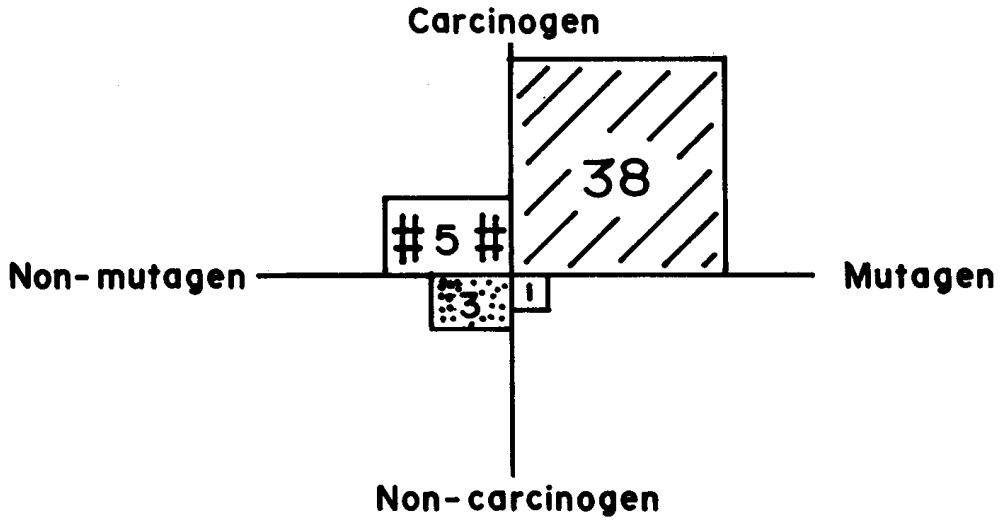


Figure 27. The physical consequences of the reaction between mutagens and DNA

trated in Figure 27.

With improved methods of mutagen detection, a big number of carcinogens have been shown to be frameshift mutagens (27). Among these are a number of polycyclic aromatic amines and N-nitrosamines (28).



Cigarette smoke, which contains a number of mutagens such as benzo(a)pyrene and other polycyclic aromatic hydrocarbons, nitrosamines, alkoxy free radicals, and cadmium, is causally associated not only with lung cancer but also with increased incidence of cancer of the oral cavity, esophagus, pancreas and bladder (29).

The mutagenicity of arsenic, chromate, aflatoxins, vinyl chloride, styrene, chlorophene, and other substances has also been established. For example, occupational exposure to or medication with arsenic has resulted in the production of skin tumor, while lung cancer has been associated with chronic arsenicism (30). Inhalation of chromate dust has induced squamous cell carcinoma and pulmonary adenoma. Aflatoxin B_1 and G_1 have long been associated with liver cancer (31). Recent epidemiological studies suggest that therapy with estrogens may contribute to the occurrence of cancers of the breast and the uterine endometrium (32). This may have some bearing on the ease by which estrogenic compounds are metabolically oxidized by the enzyme of cyctochrome P-448 (33). Occupational exposure to benzene has been linked with leukemia (34). Beta naphthylamine is known as a potent bladder carcinogen (35). Occupational exposure to vinyl chloride has resulted in angiosarcoma (36). Its mutagenic effects on the sperm cells of workers in a polyvinyl chloride plant have been associated with a number of fetal deaths during pregnancy of the workers' wives (37). Disturbances in spermatogenesis of chloroprene workers after six to ten years of work have been associated with the greater frequency of abortion among wives of chloroprene workers. Also, spontaneous abortion among women working in operating rooms have been recorded as being a consequence of the inhalation of the anesthetic halothane. All these strongly suggest that alkylating agents affecting sperm cells can induce sterility.

Effects on the DNA of germ cells may also lead to gross malformations and functional defects such as molecular abnormality of the hormone, immune, and brain functions. Of greater concern is the fact that several of these mutagens induce effects in the germ cell that can be passed from one generation to the next. It is not surprising that increasing numbers of genetic diseases have been associated with increasing modern human societies.

Teratogenic effects have also been induced by some mutagens (38). The first major human teratogen was ionizing radiation; women who were exposed to ionizing radiation at Hiroshima and Nagasaki gave birth to infants with a small head size and who were subsequently afflicted with mental retardation.

CO-MUTAGENESIS AND CO-CARCINOGENESIS

Pyrolytic products of tryptophan (Figure 28) have been isolated from the charred portion of broiled fish meats.

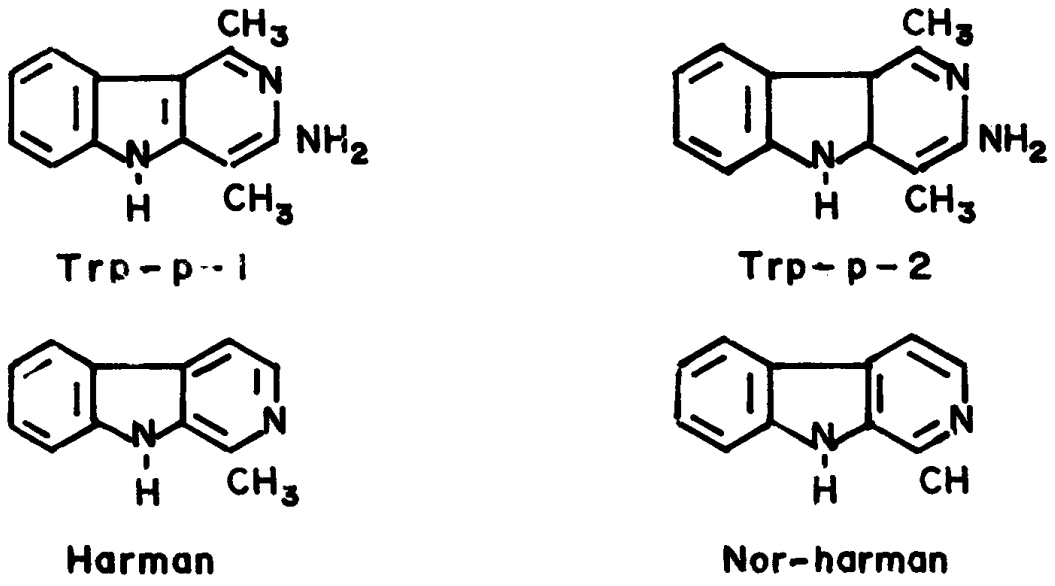


Figure 28. The pyrolytic products of tryptophan

Among these, Trp-p-1 and Trp-p-2 have been shown to be very strongly mutagenic. Harman and norharman are non-mutagenic; however, they are co-mutagenic with the cancer-causing compounds benzo (a) pyrene (a polycyclic aromatic hydrocarbon) and 2-acetylaminofluorene (an aromatic amine), i.e., they enhance the mutagenicities of these two carcinogens (39).

Sodium chloride, a non-mutagen and non-carcinogen has been shown to enhance the carcinogenicity of 4-nitro quinoline oxide and N-methyl-N-nitrosoguanidine. This effect is thought to arise from the ability of NaCl to modify the conformation of the proteoglycans of the mucosal barrier, thereby making the stomach lining more permeable to the carcinogens (40). Co-mutagenic effects of bisulfite with amines, bisulfite with semicarbazide, amines and nitrites have also been reported (41). Alkanes are not mutagenic but these have been shown to enhance the carcinogenicity of methylazoxymethanol. The alkanes used were n-decane, n-dodecane and n-tetradecane (42). Acrolein which is also found in cigarette smoke enhances benzo (a) pyrene, carcinogenesis. Table 1 lists possible sources of mutagens.

STUDIES ON ENVIRONMENTAL MUTAGENESIS IN THE PHILIPPINES

In the Philippines, studies on the mutagenicity and clastogenicity of some medicinal plants and a number of environmental chemical systems have been conducted.

Chloroform has been shown to possess DNA-damaging ability after metabolism, exhibiting clastogenic effects on the bone marrow cells of mice (43). Its mutagenic and clastogenic effects were observed to have been reduced in the presence of Vitamin E.

Formaldehyde at a level used in textile finishes has also been shown to alter not only the structure of sperm DNA but also yeast RNA (44). Methylene bis-adenosine products were observed.

Studies on antihypertensive drugs containing reserpine have revealed that reserpine, before metabolic activation induces frameshift mutations in *Salmonella typhimurium* mutants (45). In mice, reserpine was observed to metabolize a base-pair mutagen and to exhibit a clastogenic or chromosome-breaking effects

which are enhanced in the presence of hydralazine and hydrochlorthiazide.

Dipyrone has also been shown to be both a base-pair and frameshift mutagen in bacterial test systems and in experimental mice (46). It was also observed to exhibit chromosome-breaking effects which, however, were greatly reduced in the presence of L-ascorbic acid.

Isoniazid, an antitubercular drug, has been found to be a direct base-pair mutagen (47). Its mutagenicity was not reduced in the presence of some B vitamins.

Structural effects on the mutagenicity potential of some drugs have been studied (48). Of the pyrazolone-containing drugs studied, only dipyrone acted as a direct mutagen. Of the antimalarial drugs, only quinacrine induced frameshift mutations without metabolic activation.

Mutagenic and clastogenic effects of safrole-containing products likewise have been studied (49). Oil of sassafras, which is known to contain high amounts of safrole was found to exhibit a high DNA-damaging capacity. It was observed to be capable of inducing base-pair mutations in *Salmonella typhimurium* mutants before and after metabolic activation.

A number of pesticides have been investigated with respect to mutagenicity and clastogenicity (50). Shelltox and Thiodan were observed to be direct base-pair mutagens. Azodrin is transformed after metabolism to a frameshift mutagen. Azodrin, Malathion, Methylparathion, Phosdrin, Sevin, Shelltox, and Thiodan were observed to exhibit clastogenic properties which, in the case of Azodrin and Thiodan, were reduced in the presence of Vitamins C and E. Sodium nitrite and streptomycin were observed to be capable of enhancing the clastogenic effects of Malathion and Methylparathion. These effects were observed to be reduced in the presence of ethanol.

Table 1. Sources of Mutagens.

1. Cigarette smoke (a very rich source of mutagens):

   Benzo(a)pyrene and other PAH
   Alkoxy free radicals
   N-nitrosamines, N-nitrosonicotine
   Acrolein
   Cadmium

2. Automotive exhausts

   Polycyclic aromatic hydrocarbons
   Lead
   Alkylating agents (ethylene dibromide)

3. Broiled meat and broiled fish

   Pyrolytic products - aromatic amines
   Polycyclic aromatic hydrocarbons

4. Moldy peanuts and moldy grains

   Aflatoxins
   Sterigmatocystin

5. Chlorinated water

   Chloroform and other halogenated organic compounds

6. Pesticides

   DDT and its metabolites
   Dichlorvos
   Formaldehyde
   Ethylene oxide
   Eldrin
   Dieldrin
   Ziram
   Ferbam
   PCB
   Folpet
   Malathion
   Captafol
   Captan
   Dexon
   Vamidothion
   Bis-dithane

7. Drugs

   Dipyrone
   Hycanthone
   Nitrofurantoin
   Niridazole

Hydrazine derivatives
Aromatic amine derivatives
Contraceptive drugs

8. Hair dyes

   Aromatic amine derivatives

9. Industrial

   Vinyl chloride
   Chloroprene
   Styrene
   Benzene
   Polycyclic aromatic hydrocarbons
   Alkyl halides
   Halogenated ethers
   Halogenated phosphates
   Chloroform
   Carbon tetrachloride

10. Preserved fruits

    Bisulfite

11. Wines

    Bisulfites
    Nitrosamines

12. Natural

    Safrole in some spices
    Cycasin in cycad nuts
    Pyrrolizidine alkaloids in Senecio plants

13. Yellowed rice

14. Moldy camote

15. Polluted Air

16. Soot

17. Burning of municipal refuse, automobile tires

18. Nitrite-treated food products

19. Coal tar

The first medicinal plant to be studied was comfrey (*Symphytum officinale* Linn.). Decoctions and infusions of fresh and dried comfrey leaves were found to be neither clastogenic nor mutagenic (51). Neither were the following found to be mutagenic: Decoctions from leaves of *Citrus decomana* L., *Eucalyptus deglupta* Blume., *Moringa oleifera* Lam., *Pandanus odoratissimus* L., *Persea americana* L., *Psidium guajava* L., *Sterculea foetida* L. and *Tamarindus indica* L.; from whole plants of *Apium-graveolens* L., *Mimosa pudica* Linn., *Rosmarinus officinalis* L. and *Solanum nigrum* L.; from bark of *Mangifera indica* L., and *Michelia champaca* L.; from kernels of *Arecha catechu* L.; from the bran of *Oryza sativa* L.; and from the hair and cob of *Zea mays* L.; and infusions from the leaves of *Momordica balsamina* Blanco, the bark and leaves of *Anarcadium occidentale* L., the fruit of *Foeniculum vulgare* L., and the leaves of *Mangifera indica* L (52). Weak clastogenic effects were observed in the case of decoctions from the leaves and bark of *Pittosporum pentandrum* (Blanco) Merr., the leaves of *Plantago major* L., and *Eucalyptus deglupta* Blume, and cobs of *Zea mays* L. Infusions from leaves of *Anarcadium occidentale* L. also showed weak chromosome-breaking effects.

IS MAN HELPLESS AGAINST MUTAGENS?

Mutagens may alter bases in the region of the introns, the non-coding sections of DNA, which make up a great portion of the genetic material. Transcripts in these sections are spliced away during the post-transcriptional processing of mRNA.

Also, the human body is naturally endowed with repair systems for correcting defects in the DNA molecule whether during pre-replication, replication, and post-replication. However, these safety mechanisms should not be abused. Although most of them are error-free, some are error-prone. Additionally, the body can be protected against mutagens by protective enzymes, blood barriers, and substances which are free radical

or carbocation scavengers. Generalized reactions illustrating the scavenging system are shown in Figure 29.

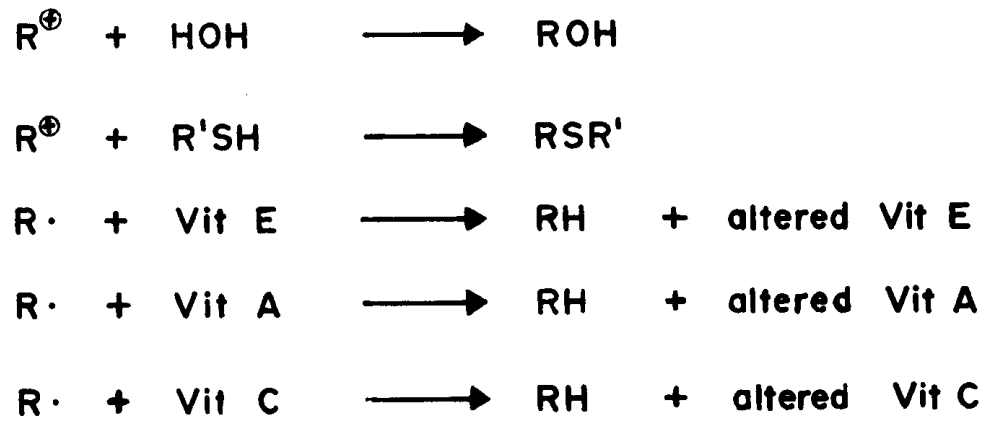


Figure 29. How some protective substances react with mutagenic free radicals and carbocations

Thus the body can be protected by the intake of substances with antimutagenic properties such as some of the vitamins. Vitamins A, C, E, B_1 (riboflavin), and B_1 (thiamine) were observed to exhibit antimutagenic effects in bone marrow cells against metronidazole, mitomycin C, aflatoxin B1, aflatoxin G1 and dimethylnitrosamine (53). Vitamin E was also found to exhibit antimutagenic effects against chloroform and Vitamin C against dipyrone (43,46). Vitamin C has further been shown to be antimutagenic not only against alkylating agents but also against intercalators, and amine derivatives (54). Recent work in our laboratories also suggest that the B vitamins niacin, pyridoxine, biotin, and cobalamin also exhibit antimutagenic properties.

Cobalt chloride reduced MNNG-induced mutations in *Escherichia coli* (55). Kada and Mochizuki also observed the antimutagenic effects of human placental extracts on ultraviolet and ionizing radiation-induced mutations also in *E. coli* (56).

Juice prepared from cabbage, broccoli, green pepper, eggplant, apple, burdock, shallot, ginger, pineapple, and mint leaf, were found to inactivate the mutagenicity of the pyrolysis products of trytophan (57). The desmutagenic factor from cabbage extract was found to be a peroxidase possessing NADPH-oxidase activity (58). Raddish, sweet potato, grape, cauliflower, and mushrooms were also found to be moderately effective while celery, cucumber, lettuce, tomato, pumpkin, onion, red cabbage, Chinese cabbage, green asparagus, kidney bean, bean sprouts, and yam were inactive.

The mutagenicity of 1,4-dinitro-2-methylpyrrole, a compound isolated from a mixture of sorbic acid and sodium nitrite was found to be destroyed by treatment with ascorbic acid and cysteine. Chemical studies revealed that the loss of mutagenicity was due to reduction of the nitro to the amino group (59).

Hemin has also been found to be antimutagenic against Trp-p1, Trp-p2, Glu-P1, benzo(a)pyrene and aflatoxin B1. Oleic acid and linoleic acid have also shown to be antimutagenic (60).

All these findings indicate that man is not totally helpless against environmental mutagens.

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