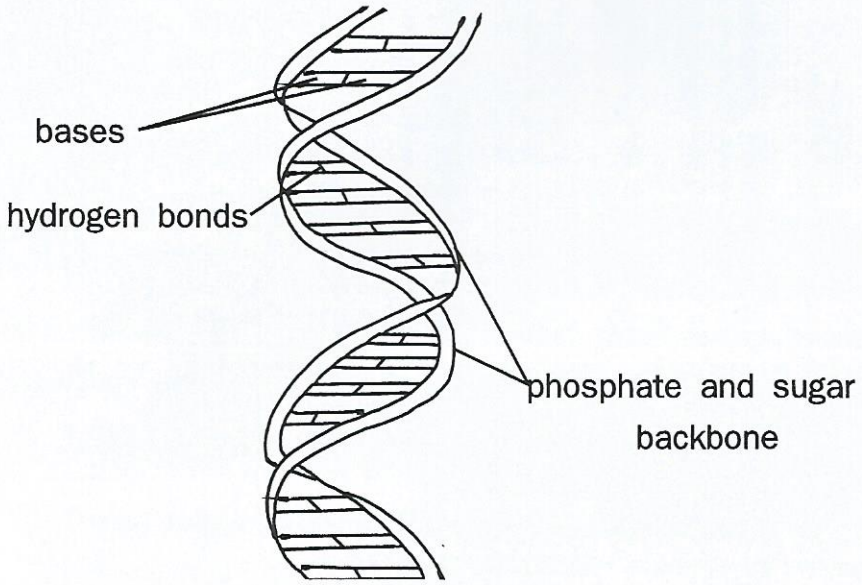

Figure 10 The structure of DNA.

of one nucleotide and the sugar of the next. The DNA molecule itself consists of two *complementary* chains of nucleotides, meaning that each nucleotide in one chain is paired opposite a specific partner in the other chain. A nucleotide containing the base cytosine will always pair with a nucleotide containing the base guanine. Likewise, a nucleotide containing adenine will always pair with a nucleotide containing thymine. The two chains are held together by hydrogen bonds which form between the pairs, and twist together in a form called a double helix (Figure 10).

The toxicants that interact with and produce changes in cellular DNA are described by the general term *mutagens*. Most mutagens interact with the base portions of nucleotides. Some may delete portions of bases, such as nitrous acid which can remove an amine group from adenine or cytosine (a process called *deamination*). Other compounds (mustard gas, for example) act as *alkylating agents*, adding alkyl groups to bases, while still others *replace* nucleotides which they closely resemble. Also, exposure to ultraviolet light and ionizing radiation can cause *cross-linking* between DNA bases. Enzyme systems exist which can deal with such damage, repairing or removing and replacing damaged nucleotides. Unrepaired damage, however, can lead to mutagenicity or carcinogenicity due to misreading or incorrect replication of DNA during cell division. These topics will be discussed in more detail in Chapter 5.

MUTAGENESIS
see also:
Carcinogenesis ***Ch. 5, p. 55***

5 CARCINOGENESIS

CARCINOGENESIS AND CANCER

Carcinogenesis is the process by which *cancer* develops in the body. Cancer is not a single disease, but rather a general term referring to many kinds of malignant growths which invade adjoining tissue and sometimes spread to distant tissues. *Carcinomas* are cancers of epithelial tissue, while *sarcomas* are cancers of supporting tissues (such as connective or muscle tissues). The most common forms of cancer are carcinomas found in skin, large intestine, bronchi, stomach, prostate gland (in males), breast (usually in females), and cervix in females.

Most current theories describe carcinogenesis as a multistep process, involving three phases beginning with change in one cell and building through an accumulation of factors to the malignant tumor. These three phases are called initiation, promotion, and progression.

Initiation is initial damage to DNA, which may be chemically induced. The initiated cell is considered to be *transformed* into a *neoplastic* cell, but remains latent until affected by promoting agents. *Promotion* is the second phase of the process during which further cellular changes lead to the development of a tumor from the initial neoplastic cell. This stage may be affected by the action of chemical promoters which stimulate cell division to produce clonal proliferation. The importance of promotion in the process of carcinogenesis should not be ignored, and in fact it has been argued that carcinogens requiring very high doses might act through cell damage and the consequential mitogenesis (cell proliferation during the repair process) rather than through any specific mechanism.

The third stage of carcinogenesis is *progression*, during which a tumor becomes malignant. *Benign* tumors are encapsulated, slowly growing, noninvasive and can be controlled by excision; *malignant* tumors are nonencapsulated, rapidly growing, invasive, disseminating, and recalcitrant to treatment. The progression to malignancy is characterized by the aggressive nature of the cells which can attach and penetrate membranes to invade new tissue. *Metastasis* is the process by which a malignant tumor invades and disseminates to other tissues.

directly inhibit sperm production. Likewise, physical agents such as *x-rays* and other forms of ionizing radiation probably cause decreases in spermatogenesis through effects on dividing cells.

Another toxicant, the pesticide *dibromochloropropane* (DBCP), caused destruction of seminiferous tubule epithelium in exposed workers, inhibiting spermatogenesis either through what may have been either effects on primary spermatogonia or through effects on Sertoli cells. The mechanism of action of DBCP in either case may be through inhibition of oxidative phosphorylation. Other toxicants which may affect energy metabolism include *dinitrobenzene*, *dinitrotoluene* (DNT), and various *phthalates* (plasticizing compounds).

CADMIUM
see also:

Cardiovascular toxicology	*Ch. 8, p. 111*
Renal toxicology	*Ch.11, p. 165*
Water pollution	*Ch. 15, p. 232*
Cadmium	*Appendix, p. 235*

LEAD
see also:

Cardiovascular toxicology	*Ch. 8, p. 114*
Neurotoxicology	*Ch. 9, p. 140, 143*
Immunotoxicology	*Ch. 12, p. 180*
Water pollution	*Ch. 15, p. 222*
Lead	*Appendix, p. 239*

Heavy metals such as *lead* and *cadmium* are well-known reproductive toxicants. Exposure to lead has been associated with infertility as well as with chromosomal damage in sperm. Cadmium can cause testicular necrosis, probably by decreasing blood flow to the testes. *Ethanol* causes delays in testicular development and may affect supporting cells. Other male reproductive toxins include the pesticides *kepone* and *DDT*, the solvent *carbon disulfide*, and even *tobacco* (smokers have higher percentages of abnormal sperm than nonsmokers).

THE FEMALE REPRODUCTIVE SYSTEM

The same basic hormonal system which controls reproduction in the male also controls reproduction in the female. GnRF is released by the hypothalamus, initiating secretion of LH and FSH by the pituitary. In the female, though, the effects of LH and FSH are to promote the syntheses of the *estrogens* and *progestins*. These hormones participate in a complex feedback system which regulates the release of GnRF, LH, and FSH.

The pair of organs in which egg production takes place are the *ovaries* (Figure 6). Early in development, several million oogonia develop in each

THE EFFECTS OF TOXICANTS ON THE FEMALE REPRODUCTIVE SYSTEM

As in the male, toxicants which interfere with the hormonal control of reproduction can impair fertility. Anesthetics, analgesics, and other drugs which interfere with either neuronal or hormonal control of hypothalamic or pituitary function prevent ovulation. *Birth control drugs* such as oral contraceptives, as well as injectable (Depo-Provera) and implantable (Norplant) contraceptives also act on this hormonal system. These drugs contain a mixture of estrogen and progestins which inhibit the release of FSH and LH and thus inhibit ovulation. Side effects associated with these drugs include some increase in risk of thromboembolism (obstruction of a blood vessel by a blood clot), myocardial infarction, and stroke. These risks increase with age and with the presence of contributing factors such as smoking and underlying cardiovascular disease. There is some evidence that users of these drugs may also experience slightly increased risk for breast, vaginal, and uterine cancers; risk for ovarian cancer, however, may actually decline.

Cytotoxic substances such as *antineoplastic agents, heavy metals, polycyclic aromatic hydrocarbons*, or *radiation* may damage oocytes, particularly in adult women. The effects of such agents depend on which stage of oocyte development is affected. Effects on mature secondary oocytes will lead to temporary infertility, with fertility being restored as new secondary oocytes develop. Partial destruction of primary oocytes, however, may lead not to immediate infertility, but to early onset of menopause (which occurs when the total pool of primary oocytes in the ovary falls below a minimum number). Total destruction of primary oocytes, though, will lead to infertility as well as to premature menopause. Nonlethal effects of these agents on oocytes include DNA damage which may lead to genetic defects in offspring.

Some of these cytotoxic toxicants (polycyclic aromatic hydrocarbons, for example) must be metabolized in order to produce toxicity. This activation can occur in the ovary, as cytochrome P450 and other enzymes involved in xenobiotic metabolism are found in ovarian tissues. Toxic PAH metabolites destroy primary oocytes, which is one possible explanation for the observation that exposure to cigarette smoke (which contains PAHs) may lead to premature menopause.

POLYCYCLIC AROMATIC HYDROCARBONS
see also:
Carcinogenesis *Ch. 5, p. 59*
PAHs *Appendix, p. 244*

Many other toxicants, including some *pesticides, chlorinated hydrocarbon solvents*, and *aromatic solvents* have also been reported to interfere with female reproductive capacity.