Mutation

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An abrupt, heritable change in genes or chromosomes manifested by changes in the phenotype (the appearance) of an organism. It is theoretically preferable to define mutations as changes in deoxyribonucleic acid (DNA) sequences, but the classical definition remains the operational definition in most circumstances. Genetic segregation and recombination, however, are not mutational processes unless aberrant. *See also:* **Deoxyribonucleic acid (DNA) (/content/deoxyribonucleic-acid-dna/186500)**

The word mutation has two common meanings, one being the process and the other the product (the altered gene or chromosome carries a mutation). The process is also called mutagenesis. An organism bearing a mutation is called a mutant. An agent that induces a mutation is called a mutagen.

The study of mutation has long occupied a central position in genetics. Mutations are the ultimate sources of variability upon which evolution acts, despite being random changes that are far more likely to harm than to improve a complicated and highly evolved organism. Laboratory reconstructions have shown that rapidly mutating microbial populations overtake slowly mutating populations when the two are mixed and placed in a new environment to which neither is fully adapted. Mutation has consistently been the most telling probe into the nature of the gene, and understanding of most aspects of biology has benefited from studies of the properties of mutant organisms. Mutation is also an important component of disease, either causing it directly (for example, through birth defects) or predisposing humans to a vast array of disorders that together constitute a substantial fraction of illnesses. Finally, deliberate selection of mutant plants and animals for economic or esthetic purposes has long been practiced, and has grown into an important aspect of genetics. With advances in molecular genetics, it is now possible to construct specific mutations at will, rather than merely selecting among an array of random mutations for the infrequent useful ones. *See also:* **Breeding (animal) (/content/breeding-animal/095000)**; **Breeding (plant) (/content/breeding-plant/095100)**

Anatomy

Although there are many sites where mutations can occur in even a single chromosome, and many mechanisms to generate them, the products of mutation can be simply cataloged in genetic terms.

Genome or ploidy mutations

The sum of a cell's genes is its genome, and ploidy refers in a general sense to the number of copies of each chromosome in

a (nondividing) cell. A cell that has accidentally doubled its number of chromosomes from the normal diploid state (two copies of each chromosome) is called tetraploid; one that has lost a single member of a normal pair is called monosomic; and one that has gained a single member of a normal pair is called trisomic. In higher animals, such changes are usually lethal or severely debilitating, the best-known human example being trisomy for chromosome 21 leading to Down syndrome (which occurs at a frequency of roughly 0.001 per birth). *See also:* **Congenital anomalies (/content/congenital-anomalies/156500)**; **Polyploidy (/content/polyploidy/436300)**

Chromosome mutations

Chromosome mutations, which alter sections composed of many DNA base pairs, consist of partial losses (deletions or deficiencies), rearrangements, and additions. Like genome mutations, most deletions that remove many genes are highly deleterious. Rearrangements may be less deleterious if they shuffle genes about but do not interrupt them or relocate them to sites where they cannot function well. They involve either inversions (simple reversals of an internal segment of a chromosome) or translocations (transfer of a segment of a chromosome to a new location). Translocations can occur within or between chromosomes, the latter often reciprocally. Even when not directly deleterious, rearrangements lead to anomalies of genetic recombination; a common secondary consequence in humans is sterility. Addition mutations are of two types, duplications and insertions. Duplications usually consist of tandem repeats of a segment of a chromosome, and may range from innocuous to lethal depending upon their location and extent. Insertions occur through the movement of special DNA sequences (transposons) that range from hundreds to thousands of DNA base pairs in length. *See also:* **Chromosome (/content/chromosome/134900)**; **Chromosome aberration (/content/chromosome-aberration/135000)**

Gene mutations

Gene mutations affect only a single gene and consist of intragenic chromosomal mutations, additions or deletions of one or a few base pairs, base-pair substitutions (point mutations), and complex mutations comprising simultaneously arising clusters of any of the above. The severity of a gene mutation depends on its individual nature and on the importance of the affected gene, and can range from innocuous to lethal.

Base-pair substitutions are divided into two groups called transitions and transversions. In transitions, such as $A \cdot T \rightarrow G \cdot C$, the purine·pyrimidine orientation is maintained; in transversions, such as $A \cdot T \rightarrow C \cdot G$, this orientation is reversed. (Here the DNA bases are denoted by A = adenine, T = thymine, G = guanine, and C = cytosine, where A and G are purines and T and C are pyrimidines; the dots indicate hydrogen bonding between bases.)

Because the genetic code employs consecutive sets of three DNA base pairs to specify consecutive amino acids in proteins, the addition or deletion of multiples of three base pairs leads to the addition or deletion of one or more amino acids. However, the addition or deletion of one or two base pairs (or any nonmultiple of three) shifts the reading frame, so that everything from that point onward is read out of its normal frame, with drastic consequences for that particular gene. These occurrences are called frameshift mutations. *See also:* **Genetic code (/content/genetic-code/284900)**

Forward and reverse mutation

Mutations from a normally functioning reference gene, chromosome, or organism to a mutant condition are called forward mutations. Their reversal by a new mutation that restores the original DNA sequence is called back mutation, or reversion. In addition, new mutations at a site distinct from a forward mutation can sometimes restore the nonmutant phenotype; these are called suppressor mutations. For instance, a base-pair addition in a protein-encoding sequence can sometimes be suppressed by the nearby deletion of a different base pair: the reading frame is restored, and the organism may no longer appear mutant if the associated amino acid changes are innocuous and the protein therefore functions normally.

Soma and germ line

In sexually reproducing multicellular animals, a mutation that arises in a somatic (body) cell cannot be passed to future generations, whereas a germ-line mutation can. Even though somatic mutations cannot harm future generations, they can be important to the individual that carries the mutant cell. They can be deadly (as by leading to cancer) or beneficial (as by generating new antibody molecules).

Scoring mutations

The rarity and sporadic nature of mutations render their study in wild organisms (that is, those in nature) very difficult. Instead, mutagenesis is studied in specialized laboratory organisms, among which microorganisms are favored because the ease of growing large populations (such as 10^9) overrides the low frequencies of mutants (such as 1 in 10^7 organisms). *See also:* **Bacterial genetics (/content/bacterial-genetics/068700)**; **Bacterial growth (/content/bacterial-growth/068800)**

In the bacterial virus T4, the circular plaques formed by viral killing of a lawn of the bacterial host have a characteristic size and fuzzy edge. Visual screening readily detects *r* mutants that make larger, sharp-edged plaques. Among these, the *rII* mutants have been widely studied because their rare revertants (and also recombinants) can be selected by growing on special bacterial hosts resistant to the parental *rII* viruses. *See also:* **Bacteriophage (/content/bacteriophage/069900)**

Among bacteria and yeasts, many biochemical traits have been used to score mutations. A frequent approach is first to obtain a mutant that requires for its growth a special nutrient, such as a vitamin or an amino acid. By growing the mutant population in a medium lacking the required growth factor, rare revertants to nutritional independence can be selected. For instance, the widely used Ames test for environmental mutagens uses mutants of the bacterium *Salmonella typhimurium* that require the amino acid histidine for growth, and the method tests for mutagens that can induce reversion.

In the fruit fly *Drosophila melanogaster*, special chromosomes are used to score induced lethal mutations on the X chromosome. Because these mutations are recessive (their effect being masked in the presence of a nonmutated chromosome) and because the X chromosome is a sex chromosome, this system screens for sex-linked recessive lethals. It is the most efficient mutation-scoring system in a higher eukaryote. *See also:* **Sex-linked inheritance (/content/sex-linked-inheritance/617600)**

Because of the difficulties of raising and examining mice by the tens of thousands under well-controlled conditions, mutation experiments are infrequently conducted with these or any other mammals. However, their chromosomal mutations can sometimes be scored by cytological (microscopal) analyses, and their gene mutations can be scored in a few systems, such as the specific-locus system in which mutations can be detected in any of seven specific genes determining, for the most part, coat-color traits. (A locus is the position of a gene on a chromosome.) The systematic study of mutation in humans is difficult for obvious reasons, and has amounted to little more than recording incidences and examining patterns of inheritance.

Mechanisms

Although important mechanisms of mutagenesis undoubtedly remain to be discovered, many, and perhaps most, of the predominant mechanisms are now known, at least in outline.

Genome mutations

Mutations that alter the number of chromosomes in a cell usually result from the faulty distribution of chromosomes during mitotic or meiotic cell divisions. The fault probably often lies in the systems of spindle fibers that segregate daughter chromosomes into daughter cells; chemicals (such as colchicine) that interfere with such fibers induce aneuploidy at high

frequencies. *See also:* **Meiosis (/content/meiosis/413500)**; **Mitosis (/content/mitosis/428300)**

Chromosome mutations

The larger of these, and probably many of the smaller as well, can be formed by chromosome breakage followed by incorrect patterns of rejoining. Many agents, including ionizing radiations and numerous chemicals, can induce chromosome breaks. As might be expected from their topology, the frequency of chromosome mutations often corresponds to the square of the dose of mutagen, that is, as "two-hit" events (two breaks plus incorrect rejoining). The mechanism of efficient rejoining of broken chromosomes is not understood, but may involve base pairing between repeated DNA sequences in the chromosome. The frequency of repeated sequences is high in the chromosomes of higher organisms, and chromosomal mutations, particularly deletions, are also frequent relative to point mutations in these organisms. In addition to events triggered by breaks, however, deletions and duplications are triggered by anomalies of genetic recombination between similar but nonhomologous DNA sequences. *See also:* **Radiation biology (/content/radiation-biology/566500)**; **Recombination (genetics) (/content/recombination-genetics/575500)**

Insertion mutations

These usually arise, not following random chromosome breaks, but through the intrinsic mobility of highly specialized DNA sequences. Called transposons, they have been found to be a major factor in spontaneous mutagenesis, because their transposition into a gene is very likely to inactivate that gene. They seem to play at most a minor role in induced mutagenesis. Transposons come in several types and sizes. Many carry repeated DNA sequences at their ends. Their mobility is often engendered by one or more of their own genes. For example, a DNA copy may be produced and then inserted elsewhere by a specialized recombination mechanism. Alternatively, the transposon may be transcribed into ribonucleic acid (RNA), copied back into DNA by a reverse transcriptase, and then inserted. *See also:* **Transposable elements (/content/transposable-elements/706750)**

Misalignment mutagenesis

This is a set of mutagenic mechanisms that proceeds through correct DNA base pairing in an incorrect (misaligned) context, generating deletions, duplications, and point mutations.

Consider two DNA sequences, identical or nearly so but separated by several to many base pairs. If the repeated sequences are sufficiently long (perhaps dozens to hundreds of base pairs) to mediate genetic recombination, then "unequal" recombination can occur, generating a duplication or a deletion or both (**Fig. 1**). Even if the repeated sequences are too short for ordinary recombination, they may still mediate anomalies of DNA metabolism that lead to duplications and deletions (**Fig. 2**): a break occurs in one of the two DNA chains, the chains separate (melt) locally, and then they reform a double helix out of register (misanneal). Subsequent DNA synthesis then closes the gap, fixing the mutation in the chromosome. In the extreme example, the DNA sequence repeat lacks intervening bases, and the additions or duplications are of only one or a few bases (generating, if occurring within a protein-coding sequence, frameshift mutations).

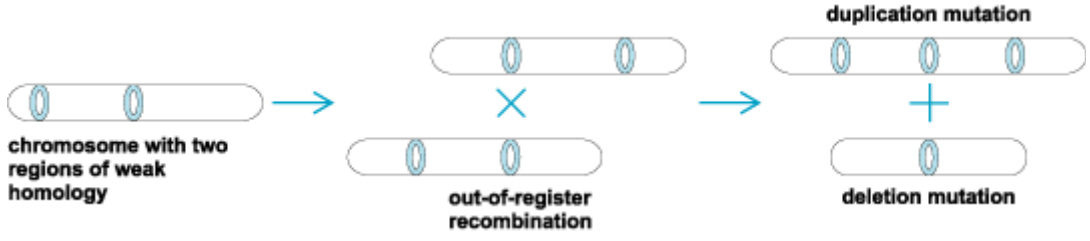

Fig. 1 Formation of duplication and deletion mutations by aberrant recombination.

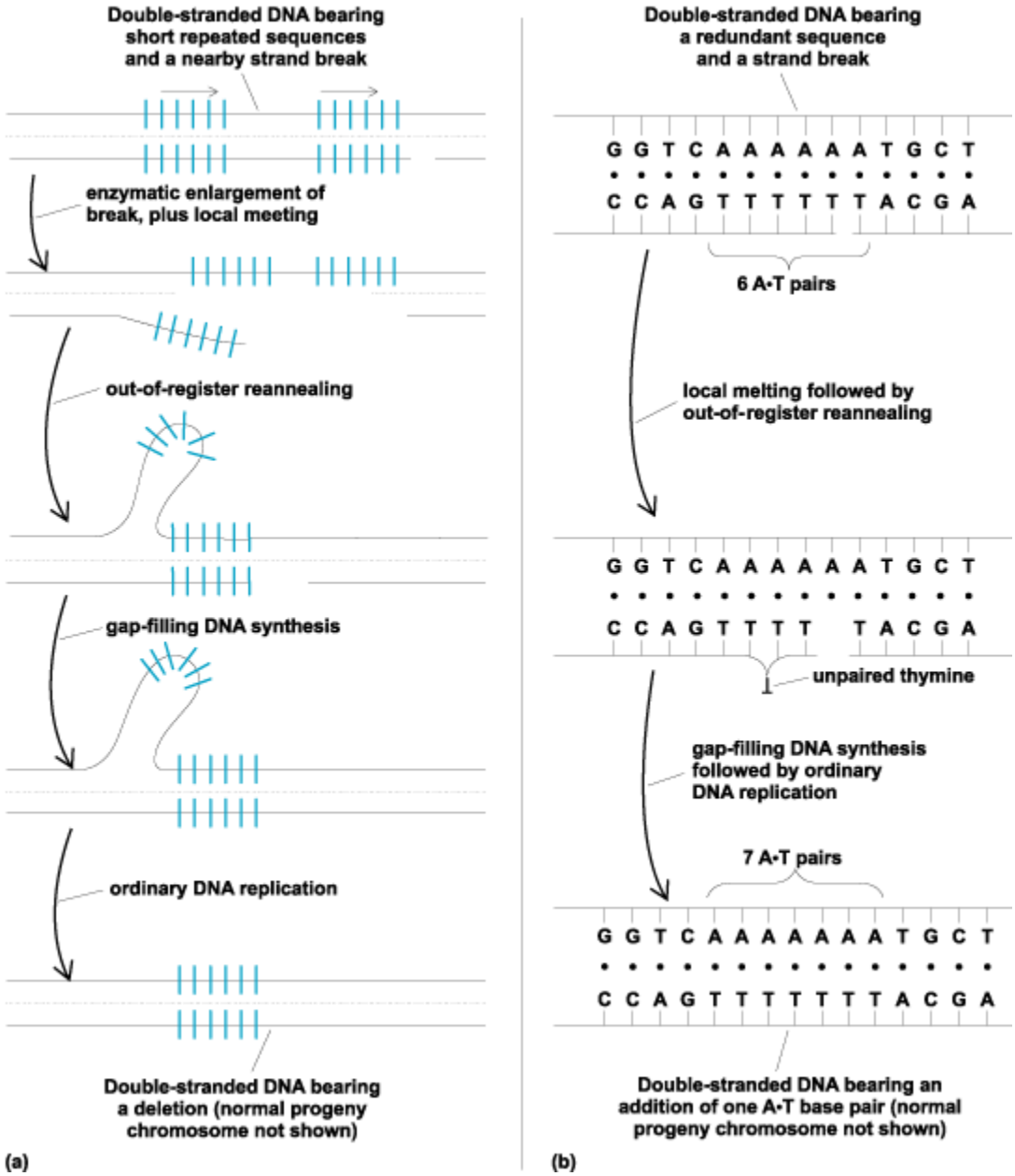

Fig. 2 Schemes for mutagenesis by misalignments within a single chromosome: (*a*) between distant repeated sequences and (*b*) within a redundant sequence. Continuous lines represent DNA sugar-phosphate backbones, and dots indicate base pairing via hydrogen bonds.

If one of the components of a repeated DNA sequence is inverted with respect to the other (both end to end and top strand to bottom strand in order to preserve the chemical polarity of DNA), the result is a DNA palindrome (a sequence that is the same when read in either direction). Just as direct repeats can mediate misalignments, so can palindromes, but with sometimes quite different consequences. For instance, during the transitory stages when DNA becomes single-stranded, as during replication, excision repair, and recombination, palindromic DNA sequences can fold back upon each other to form “hairpin” structures (**Fig. 3**). Such an anomaly can lead to a deletion, either because synthesis of the complementary strand passes by the hairpin or because the hairpin is recognized as an abnormal DNA structure and excised. In practice, while the ends of deletions often fall in either repeated or palindromic sequences, they also often fall in regions which contain both elements at once, thus providing enhanced misalignment stability.

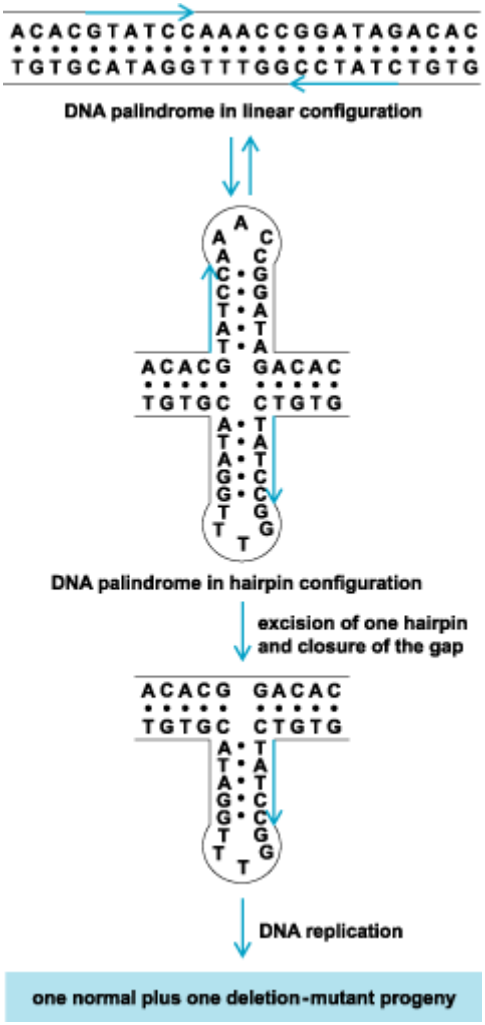

Fig. 3 Palindrome-mediated deletion mutagenesis. Color indicates palindromic sequences.

Palindromes possess an additional property, not shared with direct repeats, that causes them to mediate the formation of point mutations. Consider a palindrome which is imperfect, the inverted repeats not being perfect complements. (Here the intervening bases between the palindromic elements are irrelevant.) If it assumes a hairpin structure, then its stem will encompass mispaired or nonpaired bases (**Fig. 4**). The repair systems that maintain the structural integrity of DNA by excising damaged, abnormal, or mispaired bases can then act upon this imperfect stem, “correcting” one of its strands. The result can be base-pair substitutions, base additions or deletions, and complex mutations. (It should be noted that the mechanisms discussed here have been set in the hairpin context, but may actually occur by topologically related misalignments at DNA replication forks.)

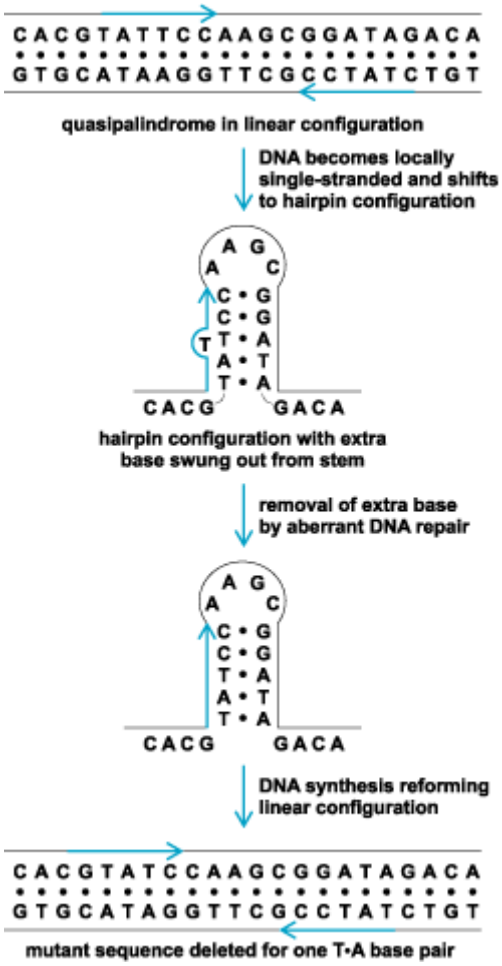

Fig. 4 Palindrome-mediated frameshift mutagenesis. Color indicates imperfectly palindromic sequences.

Mispairing mutagenesis

The normal pairing between the DNA bases (A · T and G · C) is shown in **Fig. 5***a* and *b*. DNA bases can also pair incorrectly, usually because of transient changes in base structure. An early mispairing proposal invoking base tautomers created by proton migration is shown in Fig. 5*c*. Structural studies now suggest mispairing via “wobble” configurations (Fig. 5*d*) or ionized bases (Fig. 5*e*). Note, however, that the next round of pairing by these bases is likely to be normal, generating one mutant and one nonmutant progeny DNA double helix. *See also:* **Purine (/content/purine/557800)**; **Pyrimidine (/content/pyrimidine/558900)**

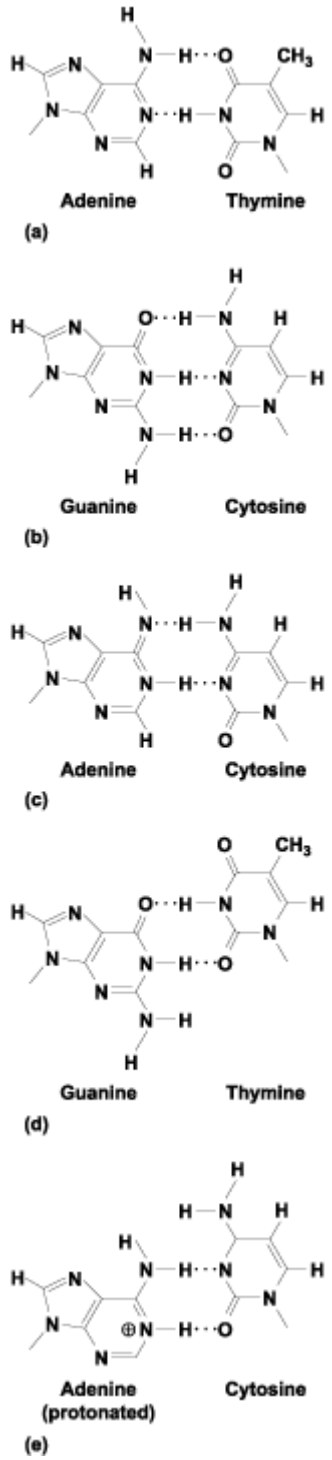

Fig. 5 Normal pairings and mispairings between the DNA bases. (*a*) The normal adenine·thymine base pair; hydrogen bonds are indicated by dotted lines and glycosidic bonds to the DNA backbone by heavy lines. (*b*) The normal guanine·cytosine base pair. (*c*) An adenine·cytosine mispair caused by proton migration in an adenine (arrow), leading to a transition mutation. (*d*) A guanine·thymine mispair involving wobble pairing. (e) An adenine·cytosine mispair involving both a protonated base and wobble pairing.

In order to generate a transversion, either two purines or two pyrimidines must mispair. In their usual configurations, however, neither such pair approximates the normal dimensions of a DNA base pair. In practice, most transversions arise via purine·purine mispairs; one example is shown in **Fig. 6**. In a normal base pair, the purines are in the *anti* configuration, which means that their hexagonal ring points toward the complementary pyrimidine. Occasionally, however, a purine (adenine in this example) rotates 180° around its glycosidic bond (the bond leading from the base to the sugar-phosphate backbone) into the *syn* configuration, thus presenting a different part of itself for potential pairing via hydrogen bonds.

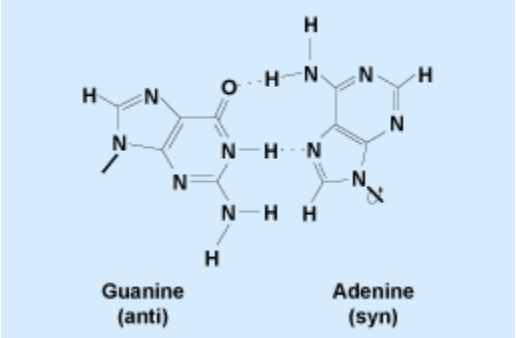

Fig. 6 A guanine·adenine mispair involving rotation of the adenine around its glycosidic bond. The mispair leads to a transversion mutation.

Chemical damage that alters the structure of a base can sometimes greatly enhance mispairing. Adding a methyl or ethyl group to the O^6 position of guanine, for instance, renders the guanine able to pair incorrectly with thymine (**Fig. 7***a*). The deamination of cytosine, which is promoted by heat and by low pH and which replaces the amino group with a keto group, generates uracil, which is identical to thymine in its base-pairing propensities (Fig. 7*b*). Thus, either of these treatments can induce G · C → A · T transitions, one via damaged guanine and the other via damaged cytosine.

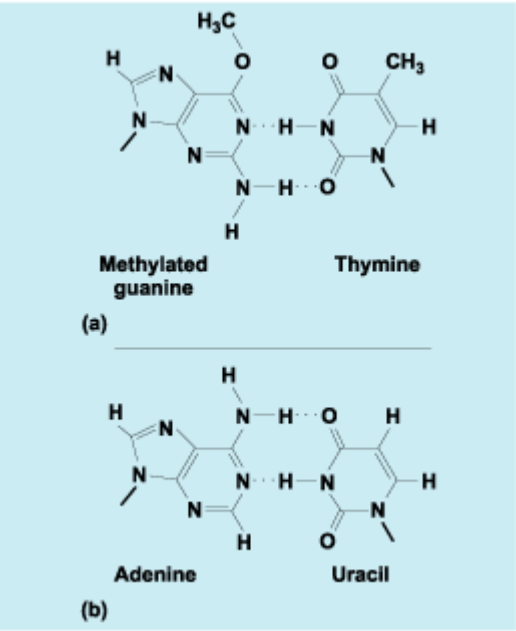

Fig. 7 Mispairing of DNA bases following chemical damage. (*a*) A guanine·thymine mispair promoted by methylation of a guanine. (*b*) An adenine·uracil mispair in which the uracil was formed by the deamination of cytosine.

Many kinds of base damage render bases unfit to pair at all. The dimerization of adjacent pyrimidines by ultraviolet irradiation, the addition of bulky groups to purines by mutagenic carcinogens such as the benzpyrines and aflatoxins, or the loss of a base (usually a purine) cause termination of DNA synthesis rather than mispairing. However, as noted below, mispairing can occur later at such a site.

Cause and prevention

Cells direct a number of repair operations against anomalies of DNA structure that would otherwise result in death or mutation. While some of these repair mechanisms circumvent death, others actually cause mutations.

Prevention

Most DNA damage is detected by excision repair systems before it can interfere with replication. These systems enzymatically remove the damaged bases and their associated sugar-phosphate backbones; the resulting gap is then filled in by DNA repair synthesis, using the complementary strand as a template. However, occasional damaged or transitorily rearranged bases enter the DNA replication fork. There they encounter DNA polymerase, the enzyme responsible for DNA synthesis. Most DNA polymerases are able to discriminate against base mispairs, although by ways that are still poorly understood. Even when a mispaired base has been covalently incorporated, however, it is often removed. This kind of repair can occur at two times. First, a 3′-exonuclease may specifically remove just-incorporated but mispaired nucleotides (nucleotide = base + sugar-phosphate). This enzymatic activity is called proofreading. Second, the few errors that escape proofreading may still be caught by a subsequent mismatch correction system. This system is remarkable in distinguishing between parental and progeny bases in newly synthesized DNA, so that the wrong rather than the right base can be excised.

Mutagenic translesion synthesis

When base damage renders pairing impossible and DNA synthesis terminates, it often reinitiates farther on, leaving behind a gap. Such a gap opposite a useless base is very apt to be lethal, certainly to the cell that inherits the damaged chromosome. Often, however, the cell is able to call up postreplication repair systems to save itself (SOS systems). Some such systems use recombination and are relatively error-free. Others, however, appear to use error-prone translesion synthesis, which is highly mutagenic because the requisite genetic information is unavailable at the damaged site. Such bypass synthesis seems to be responsible for most mutations induced by chemicals and radiations, although perhaps not contributing substantially to spontaneous mutations.

Past and future

Enzymatic systems for preventing (and sometimes causing) mutations have long evolutionary histories, presumably dating back to the genesis of cells. Therefore, mutation rates have evolved to levels that balance the few mutations that are useful, the much greater number that are deleterious, and the investment required to further reduce error rates. In DNA-based organisms ranging from small bacteriophages to the fungus *Neurospora crassa*, this balance produces about 0.3% mutations per genome per replication; organisms with larger genomes have smaller spontaneous mutation rates per base pair. In RNA viruses, the balance produces about one mutation per genome per replication. Spontaneous mutation rates are much less widely sampled in higher organisms, but in the fruitfly there is roughly one new deleterious mutation per diploid genome per sexual generation. The large majority of these mutations, however, are only mildly deleterious, and would be unrecognizable in individual humans; they might, for instance, slightly shorten life-spans, slightly increase the frequency of infections by lowering body resistance, or affect health in other equally diffuse ways.

With the growing recognition (since about 1950) that many chemicals are mutagenic, and that many humans (between about 5 and perhaps 25%, depending on the criteria used) suffer from mutations of ancient or recent origin, much attention has been directed to discovering the mutagenic components of the environment. Many artificial chemicals are mutagenic, although these are still only a small percent of the total; and as a part of their ongoing war against predators, most plants elaborate chemicals that are mutagenic for at least some organisms. The impact of these exposures is largely unassessed, but intensive ongoing research is likely to provide some concrete answers. *See also:* **Mutagens and carcinogens (/content/mutagens-and-carcinogens/441100)**

While the search for ways to prevent unwanted mutation continues vigorously, other searches seek methods to introduce specific, predetermined, desirable mutations into organisms of economic importance. By using the methods of molecular genetics, it is now usually possible to introduce specific mutations into specific genes in order, for instance, to increase the production of some marketable product. However, this step requires considerable prior knowledge about the organism's genetic and biochemical makeup. A more distant possibility is intervention in the human germ line in order, for instance, to

cure specific genetic diseases. *See also:* **Genetic engineering (/content/genetic-engineering/285000)**; **Genetics (/content/genetics/285300)**; **Human genetics (/content/human-genetics/324600)**

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